Health Canada Santé Canada
Your health and safety... our priority. Votre santé et votre sécurité... notre priorité.

Evaluation Report ERC2012-02

Tembotrione

(publié aussi en français) **2 October 2012**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

ISSN: 1925-1238 (print)
1911-8082 (online)

Catalogue number: H113-26/2012-2E (print version)
H113-26/2012-2E-PDF (PDF version)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2012

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Table of Contents

Overview 1
  Registration Decision for Tembotrione 1
  What Does Health Canada Consider When Making a Registration Decision? 1
  What Is Tembotrione? 2
  Health Considerations 2
  Environmental Considerations 4
  Value Considerations 5
  Measures to Minimize Risk 6
  What Additional Scientific Information Is Being Requested? 6
  Other Information 7
Science Evaluation 9
1.0 The Active Ingredient, Its Properties and Uses 9
  1.1 Identity of the Active Ingredient 9
  1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product 10
  1.3 Directions for Use 11
    1.3.1 Vios G3 11
  1.4 Mode of Action 12
2.0 Methods of Analysis 12
  2.1 Methods for Analysis of the Active Ingredient 12
  2.2 Method for Formulation Analysis 12
  2.3 Methods for Residue Analysis 12
3.0 Impact on Human and Animal Health 13
  3.1 Toxicology Summary 13
  3.2 Determination of Acute Reference Dose 18
  3.3 Determination of Acceptable Daily Intake 19
  3.4 Occupational and Residential Risk Assessment 20
    3.4.1 Toxicological Endpoints 20
    3.4.2 Occupational Exposure and Risk 20
    3.4.3 Residential Exposure and Risk Assessment 22
  3.5 Food Residues Exposure Assessment 23
    3.5.1 Residues in Plant and Animal Foodstuffs 23
    3.5.2 Dietary Risk Assessment 23
    3.5.3 Aggregate Exposure and Risk 24
    3.5.4 Maximum Residue Limits 24
4.0 Impact on the Environment 25
  4.1 Fate and Behaviour in the Environment 25
  4.2 Environmental Risk Characterization 27
    4.2.1 Risks to Terrestrial Organisms 28
    4.2.2 Risks to Aquatic Organisms 31

5.0 Value 33
5.1 Effectiveness Against Pests 33
5.1.1 Acceptable Efficacy Claims for Capreno Herbicide 33
5.1.2 Rainfastness 34
5.1.3 Water Volumes 34
5.2 Phytotoxicity to Host Plants 34
5.2.1 Vios G3 34
5.3 Impact on succeeding Crops 35
5.3.1 Vios G3 35
5.4 Economics 36
5.4.1 Vios G3 36
5.5 Sustainability 37
5.5.1 Survey of Alternatives 37
5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management 37
5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance 37
6.0 Pest Control Product Policy Considerations 38
6.1 Toxic Substances Management Policy Considerations 38
6.2 Formulants and Contaminants of Health or Environmental Concern 39
7.0 Summary 40
7.1 Human Health and Safety 40
7.2 Environmental Risk 40
7.3 Value 41
8.0 Regulatory Decision 41
List of Abbreviations 43
Appendix I Tables and Figures 45
Table 1 Residue Analysis Plant and Animal Matrices 45
Table 2 Residue Analysis in Soil and Water Matrices 45
Table 3 Acute Toxicity of Tembotrione and Its Associated End-use Product 45
Table 4 Acute Toxicity of Metabolites of Tembotrione 46
Table 5 Toxicity Profile of Technical Tembotrione 47
Table 6 Toxicity Profile of Metabolites of Tembotrione 52
Table 7 Toxicology Endpoints for Use in Health Risk Assessment for Tembotrione 53
Table 8 Nature of Residues 53
Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment 60
Table 10 List of Synonyms for Tembotrione Transformation Products 61
Table 11 Fate and Behaviour in the Terrestrial Environment 62
Table 12 Fate and Behaviour in the Aquatic Environment 64
Table 13 Toxicity to Non-Target Terrestrial Species 65
Table 14 Toxicity to Non-Target Aquatic Species 68
Table 15 Screening Level Risk Assessment for Terrestrial Non-target Species 71
Table 16 Screening Level Risk Assessment for Aquatic Non-target Species 74
Table 17 Refined Risk Assessment on Non-Target Species exposed to drift of tembotrione 76

Table 18 Refined Risk Assessment on Non-Target Species exposed to runoff of tembotrione 77
Table 19 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria 77
Table 20 Alternative Herbicides for Grass and Broadleaf Weed Control in Corn 78
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications 81
Table 1 Differences Between Canadian MRLs and in Other Jurisdictions 81
References 83

Overview

Registration Decision for Tembotrione

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Tembotrione Technical Herbicide containg the technical active ingredient tembotrione and Vios G3, containing the technical grade active ingredients tembotrione and thiencarbazone-methyl to control broadleaf weeds and grasses in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Tembotrione Technical Herbicide and Vios G3.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

---

[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Tembotrione?

Tembotrine is an active ingredient in Vios G3. Vios G3 contains 350 g/L of tembotrione, as well as 70 g/L of the registered active ingredient thiencarbazone-methyl.

Vios G3 is a post-emergence herbicide that is applied to field corn using ground application equipment to control broadleaf and grassy weeds. Tembotrione inhibits the plant growth enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) in target weeds, affecting their growth and killing them in about 2 weeks.

Health Considerations

Can Approved Uses of Tembotrione Affect Human Health?

Tembotrione is unlikely to affect your health when used according to label directions.

Potential exposure to tembotrione may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100 times higher (and often much higher) than levels to which humans are normally exposed when tembotrione products are used according to label directions.

The technical grade active ingredient Tembotrione was found to be a potential dermal sensitizer and requires the statement "Potential Skin Sensitizer" on the label.

The end-use product Vios G3 was mildly irritating to the eye. For this reason, the statement "Caution - eye irritant" is required on the label.

Tembotrione was not genotoxic. There was no evidence of carcinogenicity in the mouse. However, in long-term studies, there was evidence that tembotrione caused squamous cell carcinomas in the eye in rats due to long-term effects on that organ. There were indications that tembotrione potentially caused damage to the nervous system in rats and dogs at doses that caused other effects in test animals. The main signs of toxicity in animals given daily doses of tembotrione over longer periods of time were white areas on the eyes and keratitis-related changes to the cornea, mild haemorrhagic changes and liver, kidney and pancreatic changes. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When tembotrione was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother. However, since effects in the fetus were of a more severe nature than those seen in the mother, the fetus is considered more sensitive to tembotrione than the adult animal. Because of this observation, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to tembotrione.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants, the subpopulation which would ingest the most tembotrione relative to body weight, are expected to be exposed to less than 96% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from tembotrione is not of concern for all population sub-groups. Tembotrione is not carcinogenic, therefore a chronic cancer dietary risk assessment is not required.

An aggregate (food and water) dietary intake estimate for the highest exposed population (infants) was 136% of the acute reference dose. However, this is considered acceptable, since the estimation is highly conservative and the use of tembotrione in Vios G3 has been granted a 3 year conditional registration pending the submission of additional environmental studies to refine the dietary exposure to water.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using tembotrione on corn were acceptable to support the domestic uses. No new MRLs in/on corn are recommended at this time as MRLs for corn (field, sweet and pop) were previously recommended to cover residues in imported commodities. The MRLs for this active ingredient in animal commodities as a result of domestic use on field corn can be found in the Science Evaluation of this document.

Occupational Risks From Handling Vios G3

Occupational risks are not of concern when Vios G3 is used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Vios G3, as well as field workers re-entering freshly treated fields, can come in direct contact with tembotrione residues on the skin or through inhalation of spray mists.

Therefore, the label will specify appropriate personal protective equipment such as long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes, chemical-resistant coveralls, goggles or faceshield, or engineering controls for anyone conducting specific tasks with the end-use product. In addition, restrictions on the amount of product handled per day, and restricted-entry intervals for certain post-application activities are required. Taking into consideration these label requirements, risks to agriculture workers are not of concern.

For bystanders, exposure is expected to be much less than that of field workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Tembotrione Is Introduced Into the Environment?

Tembotrione is highly mobile and exhibits variable persistence in soil. It is considered to have the potential to leach. Specific information is required to understand the extent of its persistence in different kinds of soils and the potential risk of leaching to groundwater. Tembotrione is toxic to small mammals, terrestrial plants, freshwater vascular plants, and estuarine/marine invertebrates. Tembotrione poses a negligible risk to earthworms, honey bees, birds, freshwater invertebrates, freshwater and marine fish, and freshwater and marine algae.

Tembotrione exhibits variable persistence in both soil and water. The abiotic processes of hydrolysis, phototransformation and volatilization are not significant transformation/dissipation pathways. Tembotrione residues are not expected to be present in the atmosphere, nor is long-range aerial transport expected as a result of volatilization. The octanol-water partition coefficient (log K_{ow} -1.07 at pH 7) indicates that there is limited potential for bioaccumulation in organisms.

Tembotrione is stable to anaerobic biotransformation in the terrestrial environment. Aerobic biotransformation in soil is an important transformation route, though tembotrione transforms at significantly different rates in different soils. Based on submitted information, it was determined that the 80^{th} percentile of the aerobic soil biotransformation half-life values was 127 days. Laboratory studies indicate that tembotrione is expected to have high to very high mobility in soils. Since the p*K*a is 3.2, tembotrione is expected to be dissociated into its anionic form at environmentally relevant pH, and is therefore more likely to leach in neutral to alkaline soils.

Tembotrione is very highly soluble in water (28.3 g/L at pH 7). In aquatic systems, it is stable to hydrolysis and anaerobic biotransformation. In aerobic aquatic biotransformation studies, tembotrione partitioned from water into the sand or sediment. The biotransformation half-lives ranged from 64–222 days in the water/sediment systems. The environmental risk assessment for tembotrione was conducted with a tembotrione alone product at a seasonal rate of 184.8 g/ha per year. At the 184.8 g/L rate, tembotrione is expected to reach ground water. However, the rate of tembotrione applied with Vios G3 is 38.5 g/ ha year.

In the terrestrial field dissipation study in an eco-region relevant to Canada, the dissipation half-life was 11.4 days, and tembotrione was not detected below the top 15 cm of the soil profile. Although this suggests a lack of persistence under field conditions, it is possible that leaching below the depth of interest occurred.

Tembotrione has six transformation products relevant to the environment. They are labeled M1 through M4, and M6 and M7. Though they show moderate to very high mobility in soil, they are not persistent. None of the transformation products were shown to be of ecotoxicological concern.

Non-target organisms that may be vulnerable to adverse effects resulting from potential tembotrione exposure include terrestrial plants, freshwater aquatic plants, estuarine/marine invertebrates, and small mammals.

Value Considerations

What Is the Value of Vios G3

Vios G3, a post-emergence herbicide, controls broadleaf weeds and grasses in field corn.

Vios G3 is a post-emergence herbicide for the control of certain broadleaf weeds and grasses in field corn. A single application of 46 g ai/ha Vios G3 provides control and suppression of certain weeds.

Application of Vios G3 is compatible with integrated weed management practices and with conservation tillage and conventional crop production systems. Vios G3 is a post-emergence herbicide applied after weeds have emerged. Growers can therefore better assess whether the herbicide is necessary or suitable for particular weed species. Vios G3 can be used in tank mix with glyphosate.

Although several herbicides for post-emergence control of grasses in field corn are available, they are limited to Herbicide Groups 2 and 15. Vios G3, containing tembotrione as a Group 27 Herbicide, provides Canadian corn growers with an alternative product to control grasses that are developing resistance to existing chemistries.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of Vios G3 to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with farmers, custom applicators, or fieldworkers re-entering freshly treated fields coming into direct contact with Vios G3 on the skin or through inhalation of spray mists, anyone mixing, loading and applying Vios G3 must wear appropriate personal protective equipment.

The Vios G3 label specifies that anyone mixing/loading or applying the product must wear chemical-resistant coveralls and shoes plus socks. Workers mixing/loading Vios G3 must also wear chemical-resistant gloves and protective eyewear. Workers must not apply Vios G3 Herbicide to more than 150 hectares per day. The Vios G3 label requires that workers do not enter treated fields for 12 hours after application.

In addition, standard label statements to protect against drift during application were added to the product label.

Environment

Due to the risks identified for tembotrione, specific mitigation measures are necessary to protect the environment. In order to protect terrestrial and nearby freshwater and estuarine/marine habitats, both aquatic spray buffer zones (1 m) and terrestrial spray buffer zones (10 m) have been determined to be necessary for tembotrione-containing end-use products. If tembotrione is applied in combination with other pesticides, the most restrictive spray buffer zones must be observed. Toxicity label statements are required for sensitive organisms including non-target plants, aquatic invertebrates, and small mammals.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the section 12 Notice associated with these conditional registrations.

Human Health

To further refine the dietary exposure to tembotrione residues in water, additional environmental studies are required to estimate adequate Estimated Environmental Concentration values (see below).

Environment

Assessments identified a high potential for tembotrione to leach to groundwater in certain use situations. The potential for reaching groundwater occurs under conditions reflective of major use areas. Additional data are required to aid in further characterizing the potential of tembotrione leaching to groundwater. The required data will be derived from four outdoor lysimeter studies which are to be conducted in Canada on soils with a pH range of 5.8-7 (pH measured in water).

Value

Data are required from additional field trials in which the efficacy of the tank mix of glyphosate + Vios G3 at 46 g ai/ha is directly compared to that of glyphosate + a thiencarbazone-methyl alone formulation to confirm the tembotrione value at the current rate of 38.5 g ai/ha. Data are to be generated for WSSA Group 2 resistant weeds wherever possible, in addition to broadleaf weeds.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

---

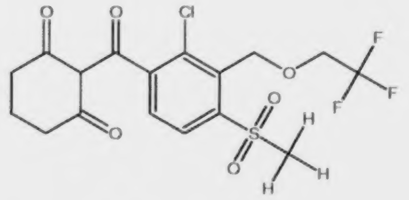
[3] As per subsection 28(1) of the *Pest Control Products Act*.

Science Evaluation

Tembotrione

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Tembotrione
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2-{2-chloro-4-mesyl-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl}cyclohexane-1,3-dione
2. Chemical Abstracts Service (CAS)	2-[2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoyl-1,3-cyclohexanedione
CAS number	335104-84-2
Molecular formula	$C_{17}H_{16}ClF_3O_6S$
Molecular weight	440.82
Structural formula	 O O Cl O F F F O O S O H H H
Purity of the active ingredient	96.15% nominal

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—Tembotrione Technical Herbicide

Property	Result
Colour and physical state	Beige powder
Odour	None
Melting range	117°C
Boiling point or range	N/A – product decomposes
Relative density	1.56
Vapour pressure	Temperature (°C) Vapour pressure (mPa) 20 1.1×10^{-5} 25 2.9×10^{-5} 50 2.6×10^{-3}
Henry's law constant at 20°C	1.69×10^{-6} Pa × m^3/mol at 20°C
Ultraviolet (UV)-visible spectrum	medium λ_{max} (nm) molar abs. (L/mol*cm) neutral 203 3.10×10^4 acidic 205 3.10×10^4 basic 258 2.21×10^4
Solubility in water at 20°C	pH Solubility (g/L) 4 0.22 6.5 29.0
Solubility in organic solvents at 20°C	Solvent Solubility (g/L) n-hexane 0.0476 ethanol 8.2 toluene 75.7 ethyl acetate 180.2 acetone 300–600 dichloromethane >600 dimethyl sulfoxide >600
n-Octanol–water partition coefficient (K_{ow})	pH log K_{ow} 2 2.16 7 -1.09 9 -1.37
Dissociation constant (pK_a)	3.2
Stability (temperature, metal)	Stable to temperatures up to the melting point, and to metals and metal ions

End-use Product— Vios G3

Property	Result
Colour	Tan
Odour	Paint like odour
Physical state	Viscous liquid
Formulation type	Suspenion
Guarantee	Tembotrione..................350 g/L nominal Thiencarbazone-methyl.......70 g/L nominal
Container material and description	1 L High density polyethylene (HDPE) bottles/jugs
Density	1.2347 g/mL
pH of 10% dispersion in water	3.16
Oxidizing or reducing action	Product does not contain oxidizing or reducing agents
Storage stability	Storage stability will be submitted upon completion
Corrosion characteristics	Not expected to be corrosive to storage container, data will be submitted with the storage stability study.
Explodability	Product does not have explosive potential

1.3 Directions for Use

1.3.1 Vios G3

Vios G3, containing 350 g/L tembotrione and 70 g/L thiencarbazone-methyl, is a selective herbicide for use as a post-emergence treatment alone in field corn or in tank mixture with glyphosate on glyphosate tolerant corn, in eastern Canada only. The product is applied once per growing season, to corn at the 1-6 leaf stage, at a rate of 110 mL/ha Vios G3 (total 46 g a.i./ha) (Table 1.3.1.1) as a broadcast treatment with ground application equipment only.

Table 1.3.1.1 Rates of Application for Vios G3

Herbicide Rate	For Residual Control of the Following Weeds[a]
110 mL/ha Vios G3 (total 46 g ai/ha)	Lamb's quarters, redroot pigweed, wild buckwheat, lady's thumb, wild mustard, common hempnettle, common chickweed, green foxtail, yellow foxtail, barnyard grass, witchgrass
110 mL/ha Vios G3 (total 46 g ai/ha) + a labelled glyphosate partner at labelled rates	Lamb's quarters, redroot pigweed, wild buckwheat, lady's thumb, wild mustard, common hempnettle, common chickweed, green foxtail, yellow foxtail, barnyard grass, witchgrass

[a] the tank mix will not provide residual control of ALS-resistant weeds

1.4 Mode of Action

Tembotrione is classified as Group 27 Herbicide (refer to DIR99-06 for details at www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir99-06/index-eng.php). The primary mode of action of tembotrione is as an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD) in the biosynthesis of plastoquinones, tocopherols and carotenoids. Blockage of the pathway at this enzymatic site leads to disturbed chloroplast synthesis and function as well as to photobleaching by oxidative degradation of chlorophyll and destruction of the photosynthetic membranes. Sensitive weed species exhibit symptoms within 2–5 days in the form of strong bleaching effects, particularly on the growing zones of the shoot. After treatment, growth is inhibited, chlorotic tissues become necrotic under the influence of light, and sensitive plants typically die within 14 days.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in technical tembotrione have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredients in the formulations have been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Analytical methods using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) and gas chromatography-mass spectrometry (GC-MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

Liquid chromatography methods with mass spectrometry (LC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70-120%) were obtained in plant and animal matrices. Adequate extraction efficiencies were demonstrated using radiolabelled corn stover, egg and beef liver samples analyzed with the enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for tembotrione was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

It is notable in the toxicology database that different species have very different toxicological outcomes in response to the administration of tembotrione.

In metabolic studies performed on rats, tembotrione was absorbed extensively, eliminated quickly and effectively and was well distributed in the body. Radiolabelled material was primarily found in the liver and kidneys of exposed animals. There were large sex differences in metabolism. Males absorbed the parent compound, primarily metabolised it via hydroxylation and excreted the compound in the bile. Females absorbed the parent compound, but excreted it unmetabolised in the urine. As dose increased, males excreted more parent in the urine and females excreted more hydroxylated compound in the faeces, however, the ratios were never equal.

Acute studies on Tembotrione Technical Herbicide found it to be of low toxicity via the oral, dermal and inhalation routes to rats. It was found to be non-irritating to the skin of rabbits and minimally irritating to the eyes. It was found to be a dermal sensitizer.

Vios G3 was of low acute toxicity by the oral, dermal and inhalation routes of exposure in Sprague Dawley rats. It was slightly irritating to the skin and mildly irritating to the eyes of New Zealand White rabbits. Vios G3 was negative for skin sensitization using the Guinea Pig Buehler method.

A plant metabolite referred to as AE 0456148 (M6), which is also a product of rat metabolism, was found to be of low toxicity via the oral and dermal routes, non-irritating to the skin, moderately irritating to the eyes and a dermal sensitiser. It was not genotoxic. In a 90-day study, the sole change was a decrease in female body weight and body weight gain at the end of the study.

A plant metabolite referred to as AE 1417268 (M5), was found to be of low toxicity in an acute oral study and non-genotoxic. In a 90-day rat study, M5 was found to increase corneal opacity and cause neovascularisation and oedema in the eyes and increase pancreatic focal/multifocal acinar degeneration/apoptosis at lower doses in males than in females.

A plant metabolite referred to as AE 1392936 (M2), was found to be of low oral toxicity and found not to be genotoxic. There were limited studies, but it was structurally similar to M5 with the substitution of an -OH group rather than a $-CF_3$ group.

The main target organs in the mouse via the oral route were the gallbladder and kidney, with liver and GI effects at higher doses. Females were more sensitive than males. In the liver, there were increased organ weights and size, an increase in dark colouration, hepatocellulary hypertrophy, a loss of heptaocellular vacuolation, increased eosinophilic inclusion bodies, ALAT activity and blood urea in males along with focal/multifocal midzonal hepatocellular necrosis, increased hepatocellular degeneration, interstitial mixed cell infiltration and a decrease in AP activity, an increase in mitosis in hepatocytes and increased hepatocellular eosinophilic foci in females. Gallstones were noted in mice. These differed from typical, cholesterol-based gallstones in that they were comprised entirely of tembotrione. Changes to the gallbladder consisted of increased eosinophilic cytoplasmic alteration, increased subepithelial mixed cell infiltrate and increased epithelial hyperplasia. Gastrointestinal changes were seen in the 90-day study, at higher doses than the 18-month study. This included dark content in the stomach and intestines and focal erosions in the stomach in females. Other changes consisted of increased multifocal unilateral periorbital neutrophilic infiltrate, increased intratubular golden brown pigmentation in the kidneys, decreased white blood cell counts and decreased red blood cell counts, haematocrit and haemoglobin in high dose females and increased dilated tubules in the epididymides in high dose males.

The target organs in the rat via both oral and dermal routes were the thyroid and pancreas, with liver, kidney and eye effects also noted with oral administration and much of the toxicity was related to an increase in plasma tyrosine, a condition referred to as tyrosinaemia. Male rats were more sensitive to changes in the eye, liver and thyroid with haemorrhagic effects occurring at high doses. Female rats were more sensitive to pancreatic effects. In the eye, there was a build-up of tyrosine causing corneal opacities and oedema, progressing to neovascularisation, epithelial cell hyperplasia, retinal degeneration, hyperkeratosis and, in rare/limited cases, squamous cell carcinomas in males dosed 200× higher than the NOAEL. Liver changes consisted of increased cholesterol and blood urea, increased sinusoid dilatation, fibrosis, extramedullary haematopoeisis, haemorrhages and hypertrophy. Thyroid changes consisted of cystic hyperplasia and increased colloid alteration. At high doses in the short-term studies, male rats were subject to blood parameter and clinical sign changes indicating anaemia and haemorrhaging. Pancreatic changes were characterised by focal/multifocal acinar atrophy/fibrosis along with chronic inflammation, chronic active inflammation and an increase in nodules/masses in females and acinar hyperplasia in males in long-term studies. The changes were more common in females than in males, with the exception of the 28-day dermal studies, where the incidence of acinar apoptosis/degeneration was slightly higher in males at low doses. Kidney changes consisted of an increase in urinary ketones, obviously large, irregular surfaced, pale and mottled kidneys, increased kidney weights, and an increase in debris and transitional cell hyperplasia, kidney dilatation, chronic inflammation and tubular basophilia. Other findings common to the rat studies at higher doses were decreased body weights, body weight gains and food consumption, decreased thymus weights, decreased food consumption, decreased blood glucose, decreased pituitary weights with an increase in pituitary cysts and hyperplasia in females, inflammation or mineralisation of peripheral nerves along with nerve and skeletal atrophy in females, increased adrenal weights in females with increased hypertrophy and necrosis and an increase in white foci and alveolar macrophages in the female lungs. Changes specific to males consisted of an increase in stomach ulcers, increased epithelial cell hyperplasia in the stomach, increased lymphoid hyperplasia of the rectum, increased exorbital gland dilatation beginning at high doses and increased polyarteritis nodosa at the LOAEL.

Dogs are slightly less sensitive to tembotrione-induced tyrosinaemia than rats, but more so than mice and humans. The target organs for the 90-day and 12-month feeding studies were the blood system including the bone marrow, the liver and the nervous system with females being more sensitive than males to the effects of the compound. There were no effects on the eyes. There were notable changes in haematology parameters indicating treatment-related anaemia. Liver changes consisted of increased liver weights, increases in mild cloudy hepatocellular swelling and golden-brown pigmentation of hepatocytes and Kupffer cells, increased ALK and decreased total bilirubin. Behavioural changes such as uncoordinated movements, decreased motor activity, abnormal posture, hopping, wheelbarrowing and placing were noted at high doses. Histopathologically, there was an increase in the number of digestion chambers in the sciatic, femoral, musculocutaneous and/or radial nerves consisting of focal enlargement of the myelin sheath filled with myelin debris. There was also focal muscle atrophy/regeneration of the tibial muscle. Changes in other organs consisted of an increase in urinary ketones and changes to the thyroid consisting of increased organ weight and increased golden brown pigmentation of the follicular cells. Generally, there was a decrease in body weight and body weight gain as well as decreased food consumption and food efficiency at high doses.

There was no evidence of teratogenicity or sensitivity of the young in the developmental studies in either the rat or the rabbit. In the rat studies, there was evidence of systemic toxicity in dams with decreased body weights and increased liver weights. At high doses, one rat dam was found to have dark content in the stomach and intestine with depressed foci in the stomach, possibly indicating haemorrhagic changes in the GI tract. Fetal toxicity was limited to the same doses as the dams and changes related to maternal toxicity, such as increases in runts, decreases in body weights and ossification delays and variations. Toxicology in the rabbit developmental studies was similar, with significant systemic toxicity in females including mortality at high doses accompanied by dark content in the intestines and ossification changes in the fetuses. The only other change in the rabbit fetuses was an increase in short or absent brachiocephalic trunks and bilaterally dilated cerebral lateral vesicles at maternally toxic doses.

Reproductive toxicity, as well as sensitivity of the young, was seen in the 2-generation reproduction study. There was a slightly decreased mean percentage of progressive spermatozoa occurring at the high dose in the F_0 generation associated with a slight decrease in mean percent motility and decreased mean total testicular sperm count. There were no treatment-related effects on reproductive performance in males, but the adverse nature of the findings could not be discounted. In females, there was a decrease in ovarian antral follicle and corpora lutea counts observed in high-dose F_1 females associated with increased numbers of primordial/preantral follicles. These findings were considered adverse due to the concern for potential onset of early senescence. In the offspring, there was a delay in preputial separation at all doses tested in the F_1 and F_2 generations and delayed vaginal opening in high-dose females. As adverse findings were observed at lower doses than adults, this indicated an increased sensitivity of rat pups following exposure. Offspring showed corneal changes earlier in development than the parental generation. However, when factoring in *in utero*, lactation and feeding exposure, pups began to show corneal changes at a time that was not inconsistent with the start of dosing. Therefore, the earlier onset of ocular effects was not considered to represent an increased sensitivity for this effect in the young.

Acute and subchronic neurotoxicity studies, and peripheral nerve pathology in rats and dogs indicated sufficient change to trigger a developmental neurotoxicity (DNT) study. In the acute study, there was a decrease in motor and locomotor activity and a decrease in arousal and rearing. In the subchronic study, there was a decrease in habituation and an increase in motor and locomotor summary session scores in males. In conjunction with the peripheral nerve atrophy and mineralisation in the carcinogenicity studies, tembotrione was considered to be a potential neurotoxicant. In the developmental neurotoxicity study, there were decreased pup body weights, decreases in the auditory startle amplitude, decreased absolute and relative brain weights and decreased brain morphometrics at the lowest dose tested, as well as an increase in the number of pups found dead following delivery and delayed preputial separation at high doses. As the auditory startle responses and brain morphometrics were at doses lower than maternal changes and reflected a more serious endpoint than was seen in maternal toxicity, the young demonstrated both a qualitative and quantitative sensitivity. A definitive NOAEL for changes in acoustic startle and decreased brain morphometry was not established. Interpretation of the brain morphometric changes were further confounded by a decrease in effect with increasing dose. This resulted in the largest changes occurring at the lowest dose and the smallest changes occurring at the highest dose that was observed in a consistent matter across the measurements. It should be noted that the DNT study contained some study limitations (i.e., lack of habituation in locomotor activity in select experimental groups; underlying concerns regarding the experimental conduct of acoustic startle, learning and memory and brain morphometric assessments). Overall, the DNT study was considered acceptable for regulatory purposes, however, there is some underlying uncertainty regarding the precision of the experimental data and the ability to characterise a dose-response for the above-noted critical effects.

There were no changes to the genotoxicity parameters in any species studied. There was a treatment-related increase in ocular squamous cell carcinomas in males at high doses. However, the eye tumours only occurred in the presence of other eye effects and there was a definite threshold effect. Therefore, a margin of exposure approach was used to estimate potential cancer risk.

The mode of action for tembotrione in mammals is the inhibition of 4-hydroxyphenylpyruvate-dioxygenase (4-HPPDase). This enzyme catalyses the conversion of 4-hydroxyphenylpyruvate (4-HPP) to homogentisate and the inhibition of the enzyme can cause a reconversion of 4-HPP to tyrosine resulting in increased plasma tyrosine levels. Activity levels of tyrosine aminotransferase (TAT), an enzyme that allows the synthesis of an alternate product, 4-hydroxyphenyl lactic acid (HPLA), when the regular tyrosine pathway is inhibited, differ greatly between species. An *in vitro* study indicated that the range of susceptibility is rats > rabbits > dogs > mice > humans with varying differences between the species. Male rats are most likely to have increased tyrosine levels and tembotrione-related tyrosinaemia due to a lack of TAT activity. Female rats have slightly more activity of the TAT enzyme and are less likely to develop tembotrione-related tyrosinaemia. Dogs and rabbits have more TAT activity than rats, but less than mice and humans. Mice have the highest levels of TAT activity of the test animals. Humans have the same amount of TAT activity as mice and are, therefore, less likely to develop compound-related tyrosinaemia. It is notable in the toxicology database that different species have very different toxicological outcomes in response to the administration of tembotrione.

The applicant submitted a number of supplementary studies and position papers concerning changes related to increased plasma tyrosine levels and the applicability of these changes to human risk assessment. They argued that, due to the large differences in TAT activity in rats, dogs, rabbits, mice and humans, that the tyrosine-induced changes not be considered relevant to human risk assessment. These changes consist of the keratitis-related changes to the eye, pancreatic effects and colloid alteration in the thyroid.

Part of the evidence submitted by the applicant was that HPPDase inhibitors, including the most powerful HPPDase inhibitor NTBC, are incapable of inducing plasma tyrosine levels to approximately 1000 µmol/L, which is the level generally accepted to be associated with tyrosine-induced changes. However, recent information indicates this level may be lower. NTBC is used therapeutically to treat Type I Tyrosinaemia in humans, a condition associated with a deficiency in fumarylacetoacetase, an enzyme further in the tyrosine metabolic pathways than HPPDase. The side-effects of treatment with NTBC include branching corneal opacities, high plasma tyrosine levels, hyperketartotic lesions on the skin of the soles and palms and nervous system damage causing mental retardation and developmental delay. In order to control the side-effects, patients are placed on a strict tyrosine-restricted diet. In one child who was noncompliant with the tyrosine-restricted diet, corneal opacities were noted when plasma tyrosine levels were between 238–602 µmol/L, considerably lower than the 1000 µmol/L level purported to be the critical level for tyrosine changes. As such, eye changes cannot be discounted in the human risk assessment until there is sufficient evidence to prove that tembotrione cannot elevate human plasma tyrosine levels to adverse levels.

It was not proven that pancreatic or colloid changes were irrelevant to human risk assessment or that they were related to increased plasma tyrosine levels. While it is generally accepted that female rats are less susceptible to increased tyrosine levels than males, pancreatic effects were seen more often in females in the oral studies than males and at levels that were lower than the generally accepted threshold for tyrosine-related changes. Pancreatic changes were also seen in the dermal studies and were seen at lower doses in males than females when administered by that route.

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, extensive data were available for tembotrione. The data consisted of prenatal developmental toxicity studies in rats and rabbits, a multi-generation reproduction study in rats and a developmental neurotoxicity study in rats. With respect to potential prenatal or postnatal toxicity, the prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to in utero exposure to tembotrione. There was evidence of sensitivity of the young in the multigeneration reproduction study in the form of decreased body weight and body weight gains at doses that did not cause similar effects in the parental animals. In addition, delayed preputial separation, minimal extramedullary haematopoeisis in the spleen, and corneal opacities, acute inflammation and neovascularisation in the eyes were observed at the lowest dose tested. In the DNT study, findings included decreased post-weaning body weights in males on PND 28 to 70, decreased acoustic startle amplitude in both sexes on PND 60 and brain morphometric changes (decreased frontal and parietal cortical thickness and cerebellum height). Interpretation of the results of this study is hampered by limitations in the study which included issues associated with study conduct, the inability to characterize a dose-response for critical endpoints and a lack of a definitive NOAEL. Changes in brain morphometrics signal a concern for prenatal and postnatal toxicity. However, this was tempered by uncertainty in the interpretation of these findings due to the atypical dose response. This information was considered in the selection of appropriate factors in the risk assessment, while remaining cognizant of the uncertainties surrounding the DNT study.

Results of the acute and chronic tests conducted on laboratory animals with tembotrione technical and its associated end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 3,4,5,6,and7 of Appendix I.

3.2 Determination of Acute Reference Dose

The recommended acute reference dose (ARfD) for tembotrione was 0.0008 mg/kg bw based on the offspring LOAEL of 0.8 mg/kg bw/d in the rat developmental neurotoxicity study. At the LOAEL, there were decreased post-weaning body weights in males on PND 28 to 70, decreased acoustic startle amplitude in both sexes on PND 60 and brain morphometric changes (decreased frontal and parietal cortical thickness and cerebellum height). This study was determined to be the most appropriate for the ARfD as it is possible that the effects could result from a single exposure. In addition, the endpoint was considered appropriate for all subpopulations including children and women of childbearing age. Uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability were applied. An additional 10× uncertainty factor was applied for extrapolating from a LOAEL to a NOAEL in the developmental neurotoxicity study. The magnitude of this factor (10×) was selected due to the uncertainties regarding the conduct of the study, including lack of dose-response in the findings. In addition, consideration was given to residual concerns regarding prenatal and postnatal toxicity, particularly the degree of concern for changes in brain morphometrics. With respect to the *Pest Control Products Act* factor, all of the required studies relevant to assessing risks to infants and children were available, however, a NOAEL for developmental neurotoxicity could not be established. The application of a 10× uncertainty factor in extrapolating from a LOAEL to a NOAEL in the critical study for endpoint selection takes into account residual uncertainties associated with this study. For this reason, the *Pest Control Products Act* factor was reduced to 1×.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{LOAEL}}{1000} = \frac{0.8\ \text{mg/kg bw}}{1000} = 0.0008\ \text{mg/kg bw of tembotrione}$$

3.3 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for tembotrione is 0.004 mg/kg bw/d based on the NOAEL of 0.04 mg/kg bw/d in the 2-year dietary rat study. The findings at the LOAEL of 0.8 mg/kg bw/d consisted of increased polyarteritis nodosa, liver and kidney alterations, keratitis of the eye, dilatation of the lacrimal gland and pigmentation changes and colloid alteration in the thyroid. This is the lowest NOAEL in the database and is protective of effects to the eye, liver, pancreas, kidney and thyroid in rats, anaemia and peripheral nerve changes in dogs and gall bladder effects in mice. Uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability were applied. With respect to the *Pest Control Products Act* factor, a margin of exposure (MOE) of 2000 exists from this ADI to the LOAEL of 0.8 mg/kg bw/d in the DNT study. For this reason, it was considered appropriate to reduce the *Pest Control Products Act* factor to 1×. This is considered adequate to address the limitations of this study and accommodate residual concerns regarding potential prenatal and postnatal toxicity. This ADI also provides a MOE of >3000 to the LOAEL of 1.3 mg/kg bw/d from the multi-generation reproduction study and of over 20 000× to the LOAEL for ocular tumours.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{100} = \frac{0.04\ \text{mg/kg bw/day}}{100} = 0.0004\ \text{mg/kg bw/day of tembotrione}$$

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term dermal and inhalation

The LOAEL of 0.8 mg/kg bw/d from the DNT study is considered the most relevant for short-term dermal and inhalation risk assessment. Worker populations could include pregnant or lactating women and therefore this endpoint was considered appropriate for occupational risk assessment. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern for this database. The target margin of exposure of 1000 includes a 10× uncertainty factor for interspecies extrapolation and a 10× uncertainty factor for intraspecies variability. It also includes a 10× uncertainty factor for extrapolating from a LOAEL to a NOAEL in the developmental neurotoxicity study. This latter factor was selected due to the uncertainties regarding the conduct of the study, including lack of dose-response in the findings. In addition, consideration was given to residual concerns regarding prenatal and postnatal toxicity, particularly the degree of concern for changes in brain morphometrics.

Occupational exposure to Vios G3 is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

3.4.1.1 Dermal Absorption

An in vivo rat study was conducted to assess the dermal absorption of a tembotrione only end-use product formulation. The most appropriate dermal absorption value for exposure assessment is considered to be 15% which includes the absorbed dose and skinbound residues. It is unlikely that all of the skinbound residues will be systemically available; thus, the value is considered conservative.

For thiencarbazone methyl, present in Vios G3, a default dermal absorption value of 100% was used, as no dermal absorption data were available.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Vios G3 (Table 3.4.2.1.1) during mixing, loading and application. Dermal and inhalation exposure estimates for workers were generated from the Pesticide Handlers Exposure Database (PHED), incorporating dermal absorption, and area treated per day values.

PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data that facilitates the generation of scenario-specific exposure estimates. The PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. Exposure estimates are presented on the basis of the best-fit measure of central tendency (in other words, summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part). For each use scenario, appropriate mixer/loader and applicator data were normalized for kg of active ingredient handled. Exposure estimates are based on unit exposure values from PHED, coupled with application rate and typical area treated per day inputs.

Exposure to workers mixing, loading and applying Vios G3 is expected to be short-to intermediate-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders/applicators applying Vios G3 to field corn crops using groundboom equipment.

Dermal exposures to tembotrione and thiencarbazone-methyl were estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposures were estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 1000 for tembotrione and 100 for thiencarbazone-methyl. As occupational endpoints for tembotrione and target MOEs for dermal and inhalation routes are identical, MOEs for all mixer/loader and applicator scenarios can be combined.

Table 3.4.2.1.1 Exposure estimates and MOEs for mixer/loader/applicators handling Vios G3

Worker	Application rate (kg ai/ha)	Area Treated per day (ha)	Exposure Scenario (Personal protective equipment; application equipment)	Combined Exposure [a] (µg/kg bw/day)	Combined MOE [b]
Thiencarbazone-methyl (Target MOE = 100)					
Farmers	0.0155	150	Liquid open mixing and loading (single layer, with gloves); groundboom, open-cab (single layer, gloves)	2.875	25 900
Custom Applicators		300		5.76	12 900
Tembotrione (Target MOE = 1000)					
Farmer or Custom Applicator	0.0385	150	Liquid open mixing and loading (chemical resistant coveralls, with gloves), groundboom, open-cab (chemical resistant coveralls, gloves) restricted area treated per day	0.80	1000

[a] **Combined Exposure Estimate = Dermal Exposure + Inhalation Exposure**

Dermal Exp Estimate = PHED Unit Exp (µg ai/kg ai handled) * Application Rate (kg ai/ha) * ATPD (ha) * dermal absorption
bw (kg) * 1000 µg/mg
And,
Inhalation Exp Estimate = PHED Unit Exp (µg ai/kg ai handled) * Application Rate (kg ai/ha) * ATPD (ha) * inhalation absorption
bw (kg) * 1000 µg/mg
where body weight = 70 kg; Dermal Absorption = 15%, Inhalation Absorption = 100%

[b] MOE = NOAEL (mg/kg bw/d)
Exposure estimate (mg/kg bw/day)

Margins of exposure for thiencarbazone-methyl are above the target of 100 for workers mixing/loading and applying Vios G3 wearing baseline personal protective equipment. For tembotrione, mitigation measures are required for workers mixing/loading and applying Vios G3 for the MOEs to reach the target of 1000. Workers mixing/loading and applying must wear chemical resistant coveralls. Mixer/loaders must wear chemical resistant gloves. No more than 150 ha may be treated per day.

3.4.2.2 Post-application Exposure and Risk

There is potential for exposure to workers re-entering areas treated with Vios G3. Since application of Vios G3 occurs early in the season (at the 1 to 6 leaf stage), scouting in low crop heights with minimum foliage is the only post-application activity that is expected to occur at this time. The duration of exposure is considered to be short-to intermediate-term, and the primary route of exposure for workers re-entering treated areas would be through dermal contact.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity specific transfer coefficients. Transfer coefficients are based on data contained in the USEPA Policy 3.1. The transfer coefficient for scouting in corn at low crop height is based on data for workers scouting in sweet corn. Chemical specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate on the day of application, and daily dissipation of 10% were used in the exposure assessment.

Exposure estimates were compared to the most relevant toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 1000 for tembotrione, and 100 for thiencarbazone-methyl.

The estimated exposure to tembotrione for workers after applying Vios G3 is 0.528 μg/kg bw/day (MOE = 1515), while the estimated exposure to thiencarbazone-methyl is 1.42 μg/kg bw/day (MOE = 52570). As such, a default restricted-entry interval (REI) of 12 hours is considered to be adequate to protect workers entering areas treated with Vios G3

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

There are no domestic class products. As residential uses are not registered, a residential exposure and risk assessment was not required.

3.4.3.2 Post-application Exposure and Risk

There are no domestic class products; therefore, a residential post-application assessment was not required.

3.4.3.3 Bystander Exposure and Risk Assessment

Bystander exposure is not quantified. Label directions are intended to minimize spray drift. Spray drift exposure to residential areas from application is considered minimal, and much less than the exposure expected for agricultural workers.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is tembotrione and the metabolite M5. The data gathering/enforcement analytical methodology, LC-MS/MS, is valid for the quantification of tembotrione residues in corn (grain, forage and stover), and livestock matrices: beef (meat, liver & kidney), poultry (muscle, liver and skin), milk, and egg. The residues of tembotrione in plant matrices are stable when stored in a freezer at -10°C for at least 188 days. Raw agricultural commodities were processed, analyses of the processed fractions showed the residues did not concentrate in the processed commodities. Supervised residue trials conducted throughout the United States and Canada using end-use products containing tembotrione at a rate higher than the rate used in Canada on field corn, popcorn and sweet corn are sufficient to support the maximum residue limits.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions were made in a refined chronic analysis: median residues of tembotrione in field corn grain, popcorn grain and sweet corn (kernel + cob with husk removed). The refined chronic dietary exposure from all supported tembotrione food uses (alone) for the total population, including infants and children, and all representative population subgroups is ≤26% of the acceptable daily intake (ADI). Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to tembotrione from food and water is 36% (0.000144 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for infants <1 year old at 96% (0.000384 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were made in a refined acute analysis: 100% crop treated, experimental processing factors, the highest average (HAFT) residue values from field corn and popcorn trials and the highest residue value from sweet corn field trials, and anticipated residues in animal commodities. The refined acute dietary exposure (food alone) for all supported tembotrione registered commodities is estimated to be <21% (0.000164 mg/kg/day) of the ARfD (95th percentile, deterministic) for the total population. Aggregate exposure from food and water is considered acceptable: 43% (0.000347 mg/kg/day) of the ARfD for the total population. The highest exposure and risk estimate is for infants <1 year old at 136% (0.001090 mg/kg bw/day) of the ARfD. The estimated environmental concentration (EEC) of water was based on a three-year conditional registration. For full registration, additional environmental data for tembotrione need to be generated to refine the dietary exposure via water.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for tembotrione consists of exposure from food and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on acute and chronic endpoints.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Liver of cattle, goats, horses and sheep	0.40
Meat byproducts (except liver) of cattle, goats, horses and sheep	0.07
Poultry, liver	0.07
Meat and fat of cattle, goats, hogs, horses sheep and poultry	0.02
Meat byproducts of hogs	0.02
Meat byproducts (except of liver) of poultry	0.02
Eggs	0.02
Milk	0.02

For additional information on maximum residue limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Tables 1, 8 and 9 in Appendix I.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Tembotrione is stable to anaerobic biotransformation in the terrestrial environment. Aerobic biotransformation in soil is an important transformation route, though tembotrione transforms at significantly different rates in different soils. Six soil biotransformation laboratory experiments were performed under aerobic conditions, and tembotrione transformed rapidly in four of these experiments (half-live values of 4.5, 5.7, 6.6, and 14.6 days) and much more slowly in the other two (127 and 194 days). Thus, it is evident that tembotrione behaves quite differently in different soils. The 80th percentile of these half-life values is 127 days. Laboratory studies of adsorption/desorption resulted in low soil adsorption coefficient or K_{oc} values (ranging from 23.0 L/kg to 92.7 L/kg), indicating that tembotrione is expected to have high to very high mobility in soils. It is postulated that both persistence and mobility are dependent on soil pH. In acidic soils ($pH < 7$; pH measured in water), tembotrione shows slower degradation and greater adsorption. Conversely, in neutral and alkaline soils ($pH > 7$; pH measured in water), tembotrione degrades more rapidly and shows less adsorption, i.e., higher mobility. Since the pKa is 3.2, tembotrione is expected to be dissociated into its anionic form at environmentally relevant pH, and is therefore more likely to leach in neutral to alkaline soils.

Data on the environmental fate and behaviour of tembotrione are summarized in Table 11 (terrestrial) and Table 12 (aquatic), Appendix I.

The abiotic processes of hydrolysis, phototransformation and volatilization are not significant pathways for the transformation and dissipation of tembotrione. Results from laboratory studies showed that tembotrione is stable to hydrolysis at environmentally relevant pH, and although phototransformation occurred, it was too slow to be an important route of transformation (soil photolysis half-life of 8.2 days, aquatic photolysis half-life of 56 days). Based on its physical-chemical properties (vapour pressure: 1.1×10^{-8} Pa at 20°C, and Henry's law constant: 1.69×10^{-6} Pa $\times$ m^3/mol at 20°C) tembotrione is not likely to volatilize from either dry or moist soils and water surfaces. Thus, tembotrione residues are not expected to be present in the atmosphere, nor is long-range aerial transport expected as a result of volatilization. The octanol-water partition coefficient of tembotrione indicates that it has a limited potential for bioconcentration in organisms (log K_{ow} -1.07 at pH 7).

Tembotrione has six transformation products relevant to the environment. They are labeled M1 through M4, and M6 and M7. (See Appendix I, Table 10 for a list of their synonyms.) All of these transformation products are present in soil. M1, M4 and M6 are present in both soil and water. M6 and M2 were the major transformation products in several of the soil types tested. M1 was a major or a minor transformation product, depending on the soil. Based on the results of laboratory studies, half-lives were observed for M2 and M3 (the major soil photolyte), and were found to be very short for M3 (< 2 days) and relatively short for M2 (7-21 days). This classifies M3 as non-persistent and M2 as slightly persistent in soil. The mobility of M6, M2 and M1 is expected to be high to very high, as indicated by low K_{oc} values for each of these transformation products observed in the laboratory studies on adsorption/desorption. The K_{oc} values for M7 indicate low to moderate mobility and the K_{oc} values for M3 indicate low to slight mobility.

Tembotrione is very highly soluble in water (28.3 g/L at pH 7). Although the use pattern of tembotrione does not include direct application to water, there is potential that aquatic systems may be exposed to tembotrione, either directly or indirectly. Tembotrione can enter the aquatic environment through spray drift and runoff from treated fields. In aquatic systems, tembotrione is stable to hydrolysis and anaerobic biotransformation. Phototransformation is not a significant contributor to the transformation of tembotrione in the photic zone (aquatic photolysis half-life of 56 days). In the aerobic aquatic biotransformation studies, tembotrione slowly partitioned from water to sediment. The biotransformation half-lives ranged from 41–139 days in sediment and 64–222 days in the water/sediment systems.

Based on the results of surface and ground water modeling, tembotrione is expected to reach ground water. When the seasonal maximum application rate of 184.8 g a.i./ha was tested using a tembotrione alone end-use product, the leaching potential was determined to be above the level of concern. Although this concern has been mitigated by using the application rate of tembotrione at 38.5 g a.i./ha per season, which is the registered rate of tembotrione for Vios G3, more information is required. Additional data are necessary to address the central issue of greater persistence and greater adsorption of tembotrione in neutral to acidic soils (pH $\leq$ 7 measured in water). These data are required to aid in further characterizing the risk of tembotrione leaching to groundwater. The required data will be derived from four outdoor lysimeter studies which are to be conducted in Canada on soils with a pH range of 5.8–7 (pH measured in water). This is the pH range at which corn is typically grown. The locations for the lysimeter studies are in Ontario and Quebec where over 90% of Canadian corn is grown.

In the terrestrial field dissipation study in an eco-region relevant to Canada, the half life was 11.4 days, and tembotrione was not detected below the top 15 cm of the soil profile. Although this suggests a lack of persistence under field conditions, it is possible that leaching below the depth of interest occurred. Two major transformation products were formed, M3 and M6, though due to storage instability, it was not possible to determine their half-lives in soil. The lack of a mass balance in a field study makes it impossible to attribute to which extent each of the dissipation and transformation processes contribute to the degradation of tembotrione. Whether tembotrione leaches or remains in the top layer of soil may be dependent not only on soil properties such as percent organic matter, texture, pH; but also on environmental characteristics such as climate and precipitation. Due to the differential chemical behaviour of tembotrione in different soils, additional information is necessary to fully characterize its fate and behaviour in the environment.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments are adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

When conducting the environmental risk assessment for tembotrione, data testing a tembotrione alone end-use product was reviewed. The tembotrione alone end use product was tested at a rate of 92.4 g tembotrione/ha applied 1-2 times per season with a minimum of 10 days between applications. This is equivalent to a maximum of 184.8 g tembotrione/ha per season. The application rate of 184.8 g tembotrione/ha per season was used in the environmental risk assessment for tembotrione.

The environmental risk assessment showed that the level of concern was not exceeded for the majority of the non-target organisms considered in the risk assessment when testing the tembotrione alone end use product at the rate of 184.8 g tembotrione/ha per season. Therefore, the environmental risk assessment was not repeated using the lower use rate of tembotrione applied with the Vios G3 end use product i.e. 38.5 g tembotrione/ha per year.

For the environmental risk assessment of thiencarbazone-methyl, please see Evaluation Report ERC2010-03, *Thiencarbazone-methyl*.

4.2.1 Risks to Terrestrial Organisms

The ecological risk assessment of tembotrione to terrestrial organisms was conducted by first evaluating the ecotoxicity data for invertebrates, vertebrates and plants (Table 13, Appendix I). One honeybee species and one earthworm species were used to represent terrestrial invertebrates. Honeybees were exposed to both the active ingredient and the tembotrione alone end-use product on an acute contact and acute oral basis, and earthworms were exposed to the active ingredient and five soil transformation products (M1, M2, M3, M6 and M7) on a short-term basis. Two bird species (using acute oral, acute dietary, and reproductive exposure) and several small mammal species (using acute gavage, short and long-term dietary exposure scenarios) were used to represent terrestrial vertebrates. Ten crop species were studied on a short-term exposure basis to the end-use product in order to represent exposure to non-target terrestrial plants. After determining the most sensitive ecotoxicity endpoints, these values were then incorporated into the deterministic risk quotient for the screening level risk assessment (Table15, Appendix I).

No mortality was observed at the highest test concentration for earthworms (100 mg ai/kg for the active ingredient and 1000 mg ai/kg for the five soil transformation products: M1, M2, M3, M6 and M7). Sublethal effects including slow reaction and body weight change were observed at concentrations above 18 mg/kg soil for tembotrione, and above 100 mg/kg for M1. No sublethal effects were observed for M2, M3, M6 and M7. The risk quotient values for tembotrione and the five soil transformation products were 0.0016 or less. Thus, the level of concern was not exceeded for earthworms.

For honey bees, the acute oral and contact toxicities were studied using both the active ingredient (tembotrione) and the tembotrione alone end-use product. All LD_{50} values (mortality) and NOEL values (damaged bees) were 84.8 g ai/bee or greater. According to the toxicity criteria presented by Atkins (et al, 1981), an LD_{50} of > 10.99 g ai/bee can be described as relatively non-toxic. When incorporated into the calculation of the risk quotient, the LD_{50} values listed above resulted in risk quotient values of 0.015 or less. Thus, the level of concern resulting from tembotrione exposure was not exceeded for honeybees.

The acute oral, acute dietary, and reproductive toxicities to birds were studied by exposing bobwhite quail and mallard duck to tembotrione. Sublethal effects observed in the bobwhite quail resulting from acute exposure included ruffled appearance and lethargy, and were observed at concentrations above 486 mg ai/kg bw. Adverse effects from dietary exposure included a reduction in the amount of body weight gain, and reproductive toxicity studies reported a reduction in the number of viable embryos/eggs set. These effects were seen at concentrations above 1890 mg ai/kg diet and 65.3 mg ai/kg diet, respectively. The LOEL for several reproductive endpoints for the bobwhite quail was 250 mg ai/kg diet. For the mallard duck, sublethal effects in the acute study included regurgitation, and in the dietary study included a reduction in food consumption, which was observed at all treatment levels. Sublethal effects on adults were also observed in the reproductive toxicity study at all the concentrations tested. Risk quotient values ranged from 0.45 for the bobwhite quail for reproductive effects (NOEC of 65.3 mg ai/kg diet), to 0.01 for the mallard duck on an acute dietary basis (LC50 > 5620 mg ai/kg diet). Thus, the level of concern resulting from tembotrione exposure was not exceeded for this group of organisms.

Wild mammals may be exposed to residues of tembotrione as a result of consumption of sprayed vegetation and/or contaminated prey. The level of concern was not exceeded for rabbits on a developmental basis, and was not exceeded for mice on a dietary basis. The most sensitive organism of the small mammals tested was the rat. Although the level of concern was not exceeded on an acute oral basis, it was exceeded for sublethal effects identified in the dietary and reproductive toxicity studies.

The risk assessment for small mammals is initially conducted at the screening level where the assumption is made that mammals are feeding exclusively on food contaminated with tembotrione. As this scenario may not necessarily represent an expected exposure under field conditions, the proportion of diet contaminated with tembotrione that would be necessary to result in a RQ of 1.0 was determined. Based on reproductive toxicity data for rats, it would require 8.9% of a small mammal's diet to be contaminated with tembotrione in order to produce adverse reproductive effects. Based on dietary toxicity data for rats, it would require 0.48% of a small mammal's diet to be contaminated with tembotrione in order to produce adverse effects resulting from dietary exposure. These percentages are quite low. It is entirely conceivable that 8.9% or 0.48% of a small mammal's diet may be contaminated with tembotrione as a result of its use as a herbicide in corn fields. Therefore, taking into account percent diet does not decrease the level of concern for small mammals on a dietary or reproductive basis.

A further characterization of the risk incorporates a refined value for the foliar dissipation half-life. The half-life is refined to 10 days based on a data set from an extensive literature review (Willis and McDowell, 1987). This results in the following risk quotient values: $RQ_{\text{rat dietary}}$: 171.3 and $RQ_{\text{rat reproductive}}$: 9.22. Thus, the level of concern is still exceeded.

The tembotrione alone end-use product was used in plant toxicity testing and was found to have effects on both seedling emergence and vegetative vigour for several plant species.

During the seedling emergence test, dry weight was significantly affected in all species with the exception of corn, ryegrass and wheat. There was a general pattern of an increase in effect with increasing test concentration, starting at the mid-range test concentrations, up to and including the highest test concentrations. For the various plant species tested, the highest test concentrations were: 10.4, 12.5, 42, 50 or 100 g ai/ha. Thus, these effects were observed at concentration ranges of 0.8–12.5 g ai/ha (lettuce), 5.2–10.4 g ai/ha (tomato) and 25–100 g ai/ha (which includes the remaining plants tested: cucumber, onion, radish, soybean, and sunflower). Plant height was significantly reduced in onion, cucumber, lettuce, radish, sunflower and tomato; however, ≥25% reductions were observed only at the highest test concentrations for lettuce (12.5 g ai/ha) and onion (100 g ai/ha). Onion was the only species to exhibit a ≥25% reduction in percent survival, relative to the negative control at the highest test concentration of 100 g ai/ha. The most sensitive monocot was onion and the most sensitive dicot was lettuce, both based on the most sensitive parameter of dry weight.

During the vegetative vigour test, corn and cucumber exhibited slight effects and all other species exhibited moderate to severe effects. A dose-response pattern was observed. Plant height was reduced relative to the negative control by ≥ 25% in all species, with the exception of corn and cucumber. Effects on plant height were observed at 1.6, 3.1 and 6.3 (tomato, sunflower), 3.1, 6.3 and 12.5 g ai/ha (lettuce, soybean), 12.5 and 25 g ai/ha (onion, radish), 50 and 100 g ai/ha (ryegrass), and 100 g a.i/ha (wheat). Lettuce and radish were the only two species in which a ≥ 25% reduction in survival was observed relative to the pooled control. For lettuce, significant reductions in survival occurred at 12.5 g ai/ha (highest test concentration for lettuce) and for radish, significant reductions occurred at 6.3, 12.5 and 25 g ai/ha (the three highest test concentrations for radish). Dry weight was significantly affected relative to the negative control (≥ 25% reduction) in all species tested, except corn. Tomato exhibited dry weight effects at all but the lowest test concentration (0.8–6.3 g a.i.ha). The most sensitive monocot species in the vegetative vigour test was onion and the most sensitive dicot was tomato, both based on the most sensitive parameter of dry weight.

In both the seedling emergence and vegetative vigour studies using the tembotrione alone end-use product, the most sensitive monocot was the onion. The seedling emergence EC_{25} of 31 g ai/ha for onion yields an RQ of 5, and the vegetative vigour EC_{25} of 5.6 g ai/ha for onion yields an RQ of 30. The most sensitive dicots were lettuce (for emergence) and tomato (for vigour), both exhibiting an EC_{25} value of 0.44 g ai/ha, yielding an RQ value of 382 for both seedling emergence and vegetative vigour. As the level of concern was exceeded for terrestrial plants exposed to the tembotrione alone end-use product, a refined assessment was conducted to determine the ecological risk resulting from runoff and/or drift of tembotrione.

During the initial screening level assessment, the terrestrial EEC value used in the risk quotient calculations is based on the assumption that exposure is derived from a direct overspray to a terrestrial habitat. In order to further characterize the risk, the exposure scenario is refined to reflect expected spray drift from a medium spray quality (6% drift), the risk quotient values for onion become 0.33 (seedling emergence) and 1.80 (vegetative vigour). Thus, the level of concern is still exceeded for vegetative vigour of the onion, once spray drift has been taken into account. The risk quotient values for lettuce and tomato both become 23 (for seedling emergence and vegetative vigour, respectively). This refinement decreases the risk quotient value for the two most sensitive dicots by an order of magnitude (382 pre-refinement to 23 post-refinement). However, the refined risk quotient value for seedling emergence of lettuce and vegetative vigour of tomato are both still greater than one. Therefore, terrestrial buffer zones greater than 1 m will be necessary in order to mitigate potential risks to non-target terrestrial vascular plants.

4.2.2 Risks to Aquatic Organisms

The ecological risk assessment of tembotrione to aquatic organisms was conducted by first evaluating the ecotoxicity data to determine the most sensitive ecotoxicity endpoints (Table 14, Appendix I). These values were then incorporated into the deterministic risk quotient for the screening level risk assessment. Risk of tembotrione to aquatic organisms was based upon evaluation of toxicity data for eight freshwater species (two invertebrates, three fish, and two algae) and four estuarine/marine species (two invertebrates, one fish and one alga) (Table 16, Appendix I).

Freshwater Organisms
For *Daphnia magna*, the 48-hour acute toxicity was studied using the active ingredient tembotrione, the transformation product M6 and the tembotrione alone end-use product. The 21-day chronic toxicity was examined using the active ingredient and the transformation product M6. The toxicity endpoints for each of the acute and chronic studies were based on immobilization. The risk quotient values range from 0.009 for tembotrione (acute) to 0.00019 for M6 (chronic). These values indicate that the level of concern for pelagic invertebrates exposed to tembotrione (represented by daphnids) is not exceeded for either acute or chronic effects.

For the chironomid (*Chironimus riparius*), the 28-day chronic toxicity was studied using the active ingredient. Using the more sensitive parameter of emergence, the risk quotient value was less than one, indicating that the level of concern for chironomids exposed to tembotrione is not exceeded for chronic effects.

The 96-hour acute toxicity to fish was studied by exposing rainbow trout to the active ingredient tembotrione, the transformation product M6 and the tembotrione alone end-use product. Tembotrione was also used in a 96-hour acute study with bluegill sunfish, and in a 34-day chronic study with fathead minnow. Risk quotient values for all freshwater fish studies ranged from 0.0021 to 0.12, indicating that the level of concern resulting from tembotrione exposure was not exceeded.

For freshwater algae, the 96-hour acute toxicity of tembotrione, and the 72-hour acute toxicity of the transformation product M6 and the tembotrione alone were examined using the green alga, *Pseudokirchneriella subcapitata*. The 120-hour acute toxicity of the active ingredient was examined using the freshwater diatom, *Navicula pelliculosa*. Risk quotient values ranged from 0.00021 for the green alga exposed to tembotrione to 0.14 for the green alga exposed to M6. The risk quotient value was also less than one for the diatom. Thus, the level of concern is not exceeded for freshwater algae.

No studies were submitted to assess the toxicity of tembotrione to amphibians. Thus, the toxicity endpoint value from the fathead minnow early life stage study was used as surrogate data. The risk quotient value calculated using the fathead for a surrogate endpoint is 0.19, indicating that the level of concern is not exceeded for amphibians.

The 7-day acute toxicity to aquatic vascular plants was studied by exposing *Lemna gibba* G3 to tembotrione and the transformation product M6. Although the level of concern was not exceeded for M6 the RQ value of 8.4 for tembotrione indicated that the level of concern was exceeded for aquatic vascular plants. Therefore, a Level 1 Assessment was conducted to determine the ecological risk resulting from runoff and/or drift of tembotrione.

Estuarine / Marine Organisms

The 96-hour acute toxicity and the 28-day chronic toxicity of tembotrione to crustaceans was examined using the mysid shrimp. Although the risk quotient value less than one on an acute basis, it was greater than one on a chronic basis. Thus, the level of concern for the mysid shrimp exposed to tembotrione on a chronic basis is exceeded. Therefore, a Level 1 Assessment was conducted to determine the ecological risk resulting from runoff and/or drift of tembotrione.

The 96-hour acute toxicity of tembotrione was also studied using the mollusk (eastern oyster), the marine fish (sheepshead minnow) and the marine diatom (*Skeletonema costatum*). Although a reduction in shell growth of eastern oyster was observed, and a reduction in cell density of the marine diatom was observed, the risk quotient values for these two organisms were less than one. For tembotrione-exposed sheepshead minnow, there was a lack of mortality and sublethal effects observed at all test concentrations. Therefore, the level of concern is not exceeded for eastern oyster, sheepshead minnow, or the marine diatom resulting from exposure to tembotrione.

In summary for the screening level for aquatic organisms, risk quotients calculated under a realistic worst-case scenario exceeded the trigger value of one for the aquatic vascular plant *Lemna gibba* G3 (representing freshwater species) and for the mysid shrimp *Americanmysis bahia* (representing marine species). Thus, a refined risk assessment was conducted taking into account both drift and runoff as these are the most likely routes of entry of tembotrione into water (Table 17 and Table 18, Appendix I). For drift, the refinement involves taking into account the actual maximum drift deposition expected from a ground boom sprayer used in corn fields at one metre downwind of a sensitive habitat (6%, assuming medium spray quality). When the exposure scenario is refined for spray drift, the acute risk quotient value for *Lemna gibba* G3 becomes 0.5, and the chronic risk quotient value for the mysid shrimp becomes 0.2. These values are both less than one, thus, the level of concern is not exceeded once spray drift has been taken into account. Thus, default buffer zones of 1m should be adequate for the protection of aquatic species from drift of tembotrione.

In order to take into account pesticide runoff, the refined assessment is conducted using the 90th percentile of modeled tembotrione concentrations which estimate runoff exposure. The resulting risk quotient value for *Lemna gibba* G3 is 2.4. Thus, use of the modeled exposure concentration results in the level of concern for effects from tembotrione run-off being exceeded on an acute basis for this freshwater plant. Using the same procedure for the saltwater mysid, the refined estimated exposure concentration for drift results in an RQ value of 1.1. Although the chronic risk to the salt water mysid is low, the level of concern is still exceeded for effects from run-off of tembotrione on chronic basis for this estuarine/marine invertebrate.

The calculated risk quotient taking into account runoff is above one for acute exposure of the freshwater plant *Lemna gibba* and the mysid shrimp *Americanmysis bahia*. Thus, label statements providing instructions to minimize runoff are required.

5.0 Value

5.1 Effectiveness Against Pests

Efficacy data were submitted from field trials conducted in 2008 at various locations in Ontario and Québec. The herbicide treatments were applied using small plot application equipment.

The efficacy of Vios G3 applied alone or in tank mix with glyphosate for the residual control of weeds was visually assessed as percent weed control and compared to the efficacy of glyphosate applied alone. Observations were made up to three times throughout the growing season.

5.1.1 Acceptable Efficacy Claims for Capreno Herbicide

The data support the weed control claims summarized in Table 5.1.1.1 when Vios G3 is applied post-emergence in field corn.

Table 5.1.1.1 Weed Control Claims for Vios G3

Herbicide Rate	Weeds Controlled
110 mL/ha Vios G3 (46 g ai/ha)	Lamb's quarters, redroot pigweed, wild buckwheat, lady's thumb, wild mustard, common hempnettle, common chickweed, green foxtail, yellow foxtail, barnyard grass, witchgrass
110 mL/ha Vios G3 (46 g ai/ha) + a labelled glyphosate partner at labelled rates	Lamb's quarters, redroot pigweed, wild buckwheat, lady's thumb, wild mustard, common hempnettle, common chickweed, green foxtail, yellow foxtail, barnyard grass, witchgrass

5.1.2 Rainfastness

Data for rainfastness for the active ingredients of Vios G3, tembotrione and thiencarbazone-methyl, were provided.

Tembotrione
One field study conducted on the Bayer Crop Science Experimental Station at Trebur, Germany in 2005 was submitted (Application 2006-3910) to support a one hour rainfastness claim. Five intervals, between herbicide application and stimulated rainfall were tested: 0, 2, 4, 6, and 8 hours. The supported rainfastness claim was two hours.

Thiencarbazone-methyl
Rainfastness of thiencarbazone-methyl has previously been determined to be one hour (refer to ER2010-03, *Thiencarbazone-methyl*.

5.1.2.1 Supported rainfastness claim

The data provided for the active ingredients of Vios G3, tembotrione and thiencarbazone-methyl, support a rainfastness claim of two hours for Vios G3.

5.1.3 Water Volumes

The data submitted for review for Vios G3 were generated in field trials in which Vios G3 was applied in the proposed spray volume range of >150 L/ha. These data support the application of Vios G3 in a minimum water volume of 150 L/ha with ground equipment.

5.2 Phytotoxicity to Host Plants

5.2.1 Vios G3

The crop safety data for Vios G3 consisted of trials in which formulations containing the individual active ingredients of Vios G3, tembotrione and thiencarbazone-methyl, were tested. The data for these formulations are acceptable in support of Vios G3.

5.2.1.1 Tembotrione

The data from nine crop tolerance trials testing a tembotrione only formulation conducted in Canada were submitted. The tolerance of field corn to sequential applications of 92 g a.i./ha tembotrione was directly compared to that of field corn to a single application of 92 g a.i./ha. A sequential treatment of tembotrione applied at the 2 × rate (i.e. 184 + 184 g a.i./ha) was also included in these trials. Intervals between the first and second applications ranged from 6 to 13 days. Considering the rate of tembotrione in Vios G3 is 38.5 g ai/ha, these data represent almost a 5× application rate. Corn grain yield, expressed as a percentage of an untreated weed-free check, was reported in 5 trials.

5.2.1.2 Thiencarbazone-methyl

The tolerance of field corn to thiencarbazone-methyl was assessed (refer to ER2010-03, *Thiencarbazone-methyl*) and found to be 30 g ai/ha. The rate of thincarbazone-methyl applied in Vios G3 is 7.7. g ai/ha.

5.2.1.3 Supported Claims

Crop injury and grain yield data for the active ingredients of Vios G3, tembotrione and thiencarbazone-methyl, support a crop tolerance claim for field corn for a single application of 110 ml/ha (46 g ai/ha) Vios G3 applied alone or in tank mixture with a labelled glyphosate partner on field corn, including glyphosate tolerant corn.

5.3 Impact on succeeding Crops

5.3.1 Vios G3

The plant back intervals for rotational crops following application of Vios G3 are summarized in Table 5.3.1.1

Table 5.3.1.1 Plant back intervals for Vios G3

Immediate plant back[a]	4 months	10 months
field corn	winter wheat	soybean, field corn

[a] In the event that a corn crop treated with Vios G3 is lost due to environmental conditions and re-seeding is required, field corn and sweet corn may be immediately reseeded.

The data for plant back interval for rotational crops following application of Vios G3 consisted of trials in which formulations containing the individual active ingredients of Vios G3, tembotrione and thiencarbazone-methyl, were tested. The data for these formulations are acceptable in support of Vios G3.

5.3.1.1 Tembotrione

Data from rotational cropping field trials were reviewed in support of a number of rotational crops including soybeans, winter wheat, and field corn, including immediate plant back of field corn. The data for tembotrione alone formulation support the plant back intervals for Vios G3.

5.3.1.2 Thiencarbazone-methyl

Rotational crops and plant back intervals for thiencarbazone-methyl has been established (refer to ER2010-03, *Thiencarbazone-methyl*). The rotational crop and plant back intervals for Vios G3 are the same.

5.4 Economics

5.4.1 Vios G3

The registration of Vios G3 would provide field corn growers with another tool for resistance management. The tank mixture with glyphosate as a post-emergence application timing provides value to field corn growers of glyphosate tolerant corn, as this would provide residual weed control in addition to early season weed control on a broad-spectrum of grassy and broad-leaved weeds with one application. The three modes of action of the Vios G3 plus glyphosate tank mix would also be an important tool to manage glyphosate tolerant volunteers (for example, glyphosate tolerant soybeans), glyphosate resistant weed species, and weeds that have been confirmed to have resistance to other herbicide groups in commercial use and the associated economic losses that accompany this increasing threat to Canadian agriculture.

According to data collected by Statistics Canada, field corn for grain and silage totalled 1,392,099 hectares in Canada in 2006. Field corn provides the greatest farm income of all the field crops in eastern Canada. In Ontario alone, the 2006 field corn crop was estimated by the Ontario Ministry of Agriculture and Food to be valued at $975 million (http://www.omafra.gov.on.ca/english/stats/crops/estimate_metric.htm).

In cropping situations, both conventional as well as in reduced or no tillage systems, it is important to provide early control of broadleaf and grassy weeds to minimize economic losses due to weed competition. Yields can be severely suppressed when weeds are not controlled. Vios G3 alone or in tank mixture with glyphosate provides the necessary short term residual control to maintain yield. The two modes of action of Vios G3 is an important tool in managing or delaying the development of resistant weeds, and controlling weeds that already exhibit herbicide resistance.

5.5 Sustainability

5.5.1 Survey of Alternatives

Vios G3 is applied post-emergence to field corn, alone or in tank mixture with glyphosate.. Although there are numerous post-emergence herbicides registered for use in field corn, Vios G3 introduces a new active ingredient to the relatively new Group 27 herbicide mode of action. Table 5.5.1 contains some alternative herbicides to Vios G3, for annual weed control in field corn.

Table 5.5.1 Alternative herbicides for annual weed control in field corn.

Active Ingredient	End Use Product	WSSA Group Number	Weeds Controlled
s-metolachlor	Dual II Magnum	15	Annual grasses
dimethenamid	Frontier	15	Annual grasses
nicosulfuron	Accent	2	Annual grasses
nicosulfuron/Rimsulfuron	Ultim	2	Anuual grasses
2,4-D	Various	4	Broadleaf weeds
dicamba	Banvel II	4	Broadleaf weeds
atrazine	Various	5	Broadleaf weeds
bromoxynil	Pardner	6	Broadleaf weeds
mesotrione	Callisto	27	Broadleaf weeds
isoxaflutole	Converge Flexx	27	Weeds
topramezone	Impact	27	Weeds
glyphosate*	Various	9	Weeds
glufosinate-ammonium*	Liberty	10	Weeds

*For use on glyphosate tolerant and glufosinate tolerant varieties, respectively.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Vios G3 offers broad spectrum weed control when applied as a post-emergence herbicide in field corn (including glyphosate tolerant varieties). It is compatible with integrated weed management practices because it controls a range of weeds with a single application and because it can control weeds both prior to and after emergence. It is compatible with both conservation tillage and conventional production systems.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting for naturally resistant biotypes. Therefore, Vios G3 should be used in rotation with herbicides having different modes of action.

The Vios G3 label includes the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action.*

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, tembotrione and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Tembotrione does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 10 for comparison with Track 1 criteria.

- Based on the available experimental data, tembotrione does not form any major transformation products in the environment that meet all Track 1 criteria.

- The formulated combination end use product Vios G3 (containing tembotrione and thiencarbazone-methyl) contains a preservative which is contaminated with 2,3,7,8-substituted PCDDs/PCDFs which have been identified in the *Canada Gazette*. The use of formulants in registered pest control products identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[2] is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[4].

---

[4] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical, and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions regarding the active ingredient tembotrione, and the formulated combination end-use product containing tembotrione and thiencarbazone-methyl:

- Technical grade tembotrione does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- No by-products or microcontaminants of health or environmental concern identified in the Canada Gazette are present in the raw materials nor are they expected to be generated during the manufacturing process of technical grade tembotrione.
- The formulated combination end use product (containing tembotrione and thiencarbazone-methyl) does not contain any formulants or contaminants at concentrations that would pose health or environmental concerns as identified in the *Canada Gazette*.

The use of formulants in registered pest control products identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[2] is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

---

[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[7] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for tembotrione is adequate to define the majority of potential toxic effects that may result from exposure to tembotrione. In subchronic and chronic studies on laboratory animals, the primary targets were the eye, liver, kidney, pancreas, thyroid, gallbladder and bone marrow. There was evidence of carcinogenicity of the rat in the eye, but only at doses where distinct eye changes were previously noted. There was evidence of increased sensitivity of the young in reproduction and developmental neurotoxicity studies. Tembotrione is a potential neurotoxicant based on peripheral nerve damage in dogs, lack of habituation in the subchronic neurotoxicity study in male rats and brain morphometric changes in the developmental neurotoxicity study. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in corn plants and animals is adequately understood. The residue definition is tembotrione and M5. The registration of Vios G3 for use on field corn can be conditionally supported. A three-year use of Vios G3 will not constitute unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. For full registration, additional environmental data for tembotrione need to be generated to refine the dietary exposure via drinking water. Sufficient crop residue data have been reviewed to recommend maximum residue limits. The PMRA recommends that the following maximum residue limits be specified for residues of tembotrione and M5 in and on liver of cattle, goats, horses and sheep (0.40 ppm); meat byproducts (except liver) of cattle, goats, horses and sheep (0.07 ppm); poultry, liver (0.07 ppm); meat and fat of cattle, goats, hogs, horses, sheep and poultry (0.02 ppm); meat byproducts of hogs (0.02 ppm); meat byproducts (except liver) of poultry (0.02 ppm); eggs (0.02 ppm); and milk (0.02 ppm).

Mixers, loaders, and applicators handling Vios G3 and workers re-entering treated corn fields in eastern Canada and Manitoba are not expected to be exposed to levels of tembotrione and thiencarbazone-methyl that will result in an unacceptable risk when Vios G3 is used according to label directions. The personal protective equipment, restricted-entry intervals, and other mitigation measures on the product label are adequate to protect workers when Vios G3 is used according to label directions.

7.2 Environmental Risk

Tembotrione poses a negligible risk to earthworms, honey bees, birds, freshwater invertebrates, freshwater and marine fish, and freshwater and marine algae. However, it is above the level of concern for small mammals, terrestrial plants, freshwater vascular plants, and marine/estuarine invertebrates. Thus, toxicity label statements, and spray buffer zones are required for any tembotrione-containing end-use products. Tembotrione is highly mobile and exhibits variable persistence in soil, and is considered a potential leacher. More information is required to elucidate the extent of its persistence in different kinds of soils and the risk of leaching into groundwater.

7.3 Value

The value data submitted in support of Vios G3 are adequate to describe its efficacy for use in field corn, including glyphosate tolerant corn. A single post-emergence application of Vios G3 at 46 g a.i./ha, alone or in tank mix with glyphosate, provides control of lamb's quarters, redroot pigweed, wild buckwheat, lady's thumb, wild mustard, common hempnettle, common chickweed, green foxtail, yellow foxtail, barnyard grass, and witchgrass.

The submitted phytotoxicity and yield data demonstrate an adequate margin of safety of field corn to Vios G3. Vios G3 also has a flexible re-cropping profile. Vios G3, containing two active ingredients, one of which is a WSSA Group 27, provides an alternative mode of action to commonly used herbicides for the labelled crop.

8.0 Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Tembotrione Technical Herbicide containg the technical active ingredient tembotrione and Vios G3, containing the technical grade active ingredients tembotrione and thiencarbazone-methyl to control broadleaf weeds and grasses in field corn.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health
To further refine the dietary exposure to tembotrione residues in water, additional environmental studies are required to estimate adequate EEC values.

Environment
The requested environmental data requirements for tembotrione consist of four outdoor lysimeter studies, which are to be conducted in Canada on soils with a pH range of 5.8–7 (pH measured in water). This is the pH range at which corn is typically grown. The requested locations for the lysimeter studies are in Ontario and Quebec where over 90% of Canadian corn is grown.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in concentration)
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RSD	relative standard deviation
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis Plant and Animal Matrices

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant	AE/03/01	Tembotrione, AE 1417268 (M5), AE 0456148 (M6), AE 1392936 (M2)	HPLC-MS/MS	0.01 ppm/analyte in field corn (forage, fodder, mature grain), sweet corn (early grain), sugarcane, turnip roots.	PMRA# 1270587 PMRA# 1270578 PMRA# 1270584 PMRA# 1270582
Animal	AE-003-A04 (beef) & AE-004-A04 (poultry)	Tembotrione	HPLC-MS/MS	0.01 ppm in beef (muscle, kidney, liver, fat), whole milk, skim milk, milk fat; poultry (muscle, liver, skin), and egg.	PMRA# 1270586 PMRA# 1270585
	Method 00967	Tembotrione, AE 1417268 (M5)	HPLC-MS/MS	0.002 ppm/analyte in milk. 0.01 ppm/analyte in beef (muscle, kidney, liver), egg.	PMRA# 1312171

Table 2 Residue Analysis in Soil and Water Matrices

Matrix	Method ID	Analyte	Method Type	MS-MS transition monitored	LOQ	References
Soil	AE002-S04-03	Parent	LC-MS-MS	439.0–402.9	10 ng/mL	1270457 1270453 1270455
		M1		316.9–140.0		
		M2		262.8–188.8		
		M3		405.0–228.2		
		M6		344.9–300.7		
		M7	GC-MS	N/A		
Water	AE005-W05-03	Parent	LC-MS-MS	439.0–402.9	0.05 ng/mL	1270456 1270458 1270454
		M2		263.0–189.0		
		M6		345.0–217.0		

Table 3 Acute Toxicity of Tembotrione and Its Associated End-use Product

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Tembotrione (Technical)				
Oral	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1346218
Dermal	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1346514
Inhalation	Rat	LC_{50} > 4.58 mg/L; Low Toxicity	No label comment	1346720

Study Type	Species	Result	Comment	Reference
Skin irritation	Rabbit	MAS[a] = 0/8; MIS[b] = 0/8; Non-irritating	No label comment	1349416
Eye irritation	Rabbit	MIS = 3.5/110 (1h); MAS = 1.33/110; Minimally irritating	No label comment	1346858
Skin sensitization	Guinea Pig	Dermal Sensitizer	Potential Skin Sensitizer	1349467
Acute Toxicity of End-Use Product				
Oral	Rat	LD_{50}♀ = 1750 mg/kg bw; Slightly acutely toxic	CAUTION - POISON	129540
Dermal	Rat	LD_{50} > 5000 mg/kg bw; Low Toxicity	No label comment	1295240
Inhalation	Rat	LC_{50} > 2.07 mg/L; Low Toxicity	No label comment	1295242
Skin irritation	Rabbit	MAS = 0.11/8; MIS = 1/8 (1h); Slightly irritating	No label comment	1295244
Eye irritation	Rabbit	MAS = 2.4/110; MIS - 15.7/110 (1h); Mildly irritating	CAUTION - EYE IRRITANT	1295243
Skin sensitization	Guinea Pig	No sensitivity	No label comment	1360083

[a] MAS = maximum average score for 24, 28 and 72 hours

[b] MIS = maximum irritation score

Table 4 Acute Toxicity of Metabolites of Tembotrione

Study Type	Species	Result	Comment	Reference
Acute Toxicity of AE 0456148				
Oral	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1346368
Dermal	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1346580
Skin irritation	Rabbit	MAS[a] = 0/8; MIS[b] = 0/8; Non-irritating	No label comment	1349449
Eye irritation	Rabbit	MAS = 15.8/110; MIS = 28.7/110 (1h); Moderately irritating		1349338
Skin sensitization	Mouse	Dermal sensitizer		1349675
Acute Toxicity of AE 1417268				
Oral	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1346462

Study Type	Species	Result	Comment	Reference
Acute Toxicity of AE 1392936				
Oral	Rat	LD_{50} > 2000 mg/kg bw; Low Toxicity	No label comment	1498000

[a] MAS = maximum average score for 24, 28 and 72 hours

[b] MIS = maximum irritation score

Table 5 Toxicity Profile of Technical Tembotrione

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
28-day dermal	Rat	Systemic toxicity: NOAEL: not established LOAEL: 250 mg/kg bw/d based on increased incidence of follicular cell hypertrophy and colloid alteration in the thyroid of males and females, and slight to moderate degenerative changes/increase of apoptotic bodies of exocrine acinar tissue in the pancreas accompanied by inflammatory infiltrates in both sexes Dermal irritation: NOAEL: 1000 mg/kg bw/d LOAEL: N/A	1359893
28-day dermal	Rat	Systemic toxicity: NOAEL: ♂ = not established; ♀ = 50 mg/kg bw/d LOAEL: ♂ = 50 mg/kg bw/d based on degeneration and apoptosis in the exocrine acinar tissue of the pancreas and increased incidence of colloid alternation in the thyroid; ♀ = 250 mg/kg bw/d based on degeneration and apoptosis in the exocrine acinar tissue of the pancreas and increased incidence of colloid alteration in the thyroid Dermal irritation: NOAEL: 1000 mg/kg bw/d LOAEL: N/A	1361240
90-day dietary	Mouse	NOAEL: 64/76 mg/kg bw/d LOAEL: 631/782 mg/kg bw/d, based on increased ALAT and blood urea in males, decreased AP in females, increased focal/multifocal midzonal hepatocellular single cell necrosis in males and increased dark livers and diffuse centrilobular hepatocellular hypertrophy in both sexes, dark content in the stomach of both sexes, focal erosions of the stomach in females and increase multifocal unilateral papilla mineralisation of the kidney in males	1383938

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
90-day dietary	Rat	NOAEL: not established LOAEL: 0.30/0.35 mg/kg bw/d, based on colloid alteration and diffuse follicular cell hypertrophy in the thyroid of males and increased urinary ketones and focal/multifocal acinar degeneration/apoptosis in the pancreas of females	1369117
90-day dietary	Rat	NOAEL: 0.07/0.08 mg/kg bw/d LOAEL: 4.45/5.59 mg/kg bw/d, based on increased corneal opacity and neovascularisation of the cornea in males and females, increased blood cholesterol in males and increased basal vacuolation of the corticotubular epithelium of the kidneys in females	1372495
90-day dietary	Dog	NOAEL: 26.7/28.5 mg/kg bw/d LOAEL: 124/111 mg/kg bw/d, based on one mortality in males, neurological clinical signs up to day 55 of the study, decreased body weight gains and food efficiency in both sexes, decreased food consumption in females, changes in haematological parameters suggestive of regenerative anaemia, liver effects and peripheral nerve histopathological findings	1323178
1-year dietary	Dog	NOAEL: ♂ = not established; ♀ = 10.2 mg/kg bw/d LOAEL: ♂ = 2.5 mg/kg bw/d, based on increased number of digestion chambers of the sciatic nerve; ♀ = 41.6 mg/kg bw/d, based on decreases in MCH and MCV, increased platelet counts and alterations in erythrocyte morphology	1319634
Carcinogenicity (18-month dietary)	Mouse	NOAEL: not established LOAEL: 4.3/5.4 mg/kg bw/d, based on gallstones, eosinophilic cytoplasmic change, subepithelial mixed cell infiltrate and dilatation in/of the gallbladder in males and females and papillary mineralisation of the kidney in females	1403429
Chronic/ Carcinogenicity (2-year dietary)	Rat - females	NOAEL: ♀ = 0.10 mg/kg bw/d LOAEL: ♀ = 1.05 mg/kg bw/d, based on corneal opacity, white areas on the eyes and keratitis-related changes in the eye, red foci in the liver, biliary hypertrophy/fibrosis, chronic liver inflammation, increased urinary ketones and pancreatic acinar atrophy/fibrosis	1305043
Chronic/ Carcinogenicity (2-year dietary)	Rat - males	NOAEL: ♂ = 0.04 mg/kg bw/d LOAEL: ♀ = 0.79 mg/kg bw/d, based on increased polyarteritis nodosa, increased cholesterol, increased sinusoid dilatation, fibrosis, extramedullary haematopoeisis, haemorrhages and hypertrophy of the liver, obviously large size, irregular surface, pale and/or mottled colouration, increased debris and transitional cell hyperplasia of the kidney and increased urinary ketones and proteins, keratitis of the eye, dilatation of the lacrimal gland, enlarged spleens, epithelial hyperplasia of the stomach and cystic hyperplasia and colloid alteration in the thyroid	1325091

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Two-generation reproduction	Rat	**Parental toxicity**: NOAEL: not established LOAEL: 1.3/1.6 mg/kg bw/d, based on corneal opacities, acute inflammation and neovascularisation of the cornea during pre-mating, gestation (F_1 only) and lactation **Offspring toxicity:** NOAEL: not established LOAEL: 1.3/1.6 mg/kg bw/d, based on decreased body weight and body weight gains, delayed preputial separation, minimal decreased extramedullary haematopoeisis in the spleen, corneal opacities, acute inflammation and neovascularisation in the eyes; indication of increased susceptibility of rat pups **Reproductive toxicity:** NOAEL: 13.1/15.4 mg/kg bw/d LOAEL: 98.2/115.4 mg/kg bw/d, based on slight decreases in sperm motility and mean testicular sperm count, and decreases in antral follicle and corpora lutea counts in the F_1 generation.	1300280
Developmental toxicity	Rat	**Maternal:** NOAEL: not established LOAEL: 25 mg/kg bw/d, based on reduced body weight in the first week of treatment **Developmental:** NOAEL: not established LOAEL: 25 mg/kg bw/d, based on increased number of runts, ossification delays in the 7th cervical centrum, 5th and 6th sternebrae and 1st metatarsals and extra ossification points on the 14th thoracic vertebrae and shortened 14th ribs	1340612
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 1 mg/kg bw/d LOAEL: 10 mg/kg bw/d, based on reduced faecal output and increased skin lesions **Developmental:** NOAEL: 1 mg/kg bw/d LOAEL: 10 mg/kg bw/d, based on extra ossification points between the atlas and axes vertebrae and on the sternebrae, ossification delays to the atlas centra and 1st and 2nd sternebrae, cartilage of the 8th rib attached to the sternum, cartilage of the 1st rib not attached to the sternum, cartilage of the 1st and 2nd ribs fused and 27 presacral vertebrae	1342796

Study Type	Species	Results^a (mg/kg/day in M/F)	Reference
Acute Neurotoxicity	Rat	NOAEL = 200 mg/kg bw/d LOAEL = 500 mg/kg bw/d, based on urine stains, red nasal staining and forepaw staining, ↓ motor and locomotor activity within one day of dosing ♂ only: ↓ arousal and rearing within one day of dosing	1426161
Subchronic Neurotoxicity	Rat	NOAEL = ♂ = 1.33 mg/kg bw/d; ♀ = 21.0 mg/kg bw/d LOAEL = ♂ = 16.4 mg/kg bw/d; ♀ = 224 mg/kg bw/d, based on ↓ habituation/↑ motor activity to week 8, ↓ BWG in males and neovascularisation of cornea; ↓ BWG in females	1334883
Developmental Neurotoxicity	Rat	**Maternal** NOAEL = 0.8 mg/kg bw/d LOAEL = 16.3 mg/kg bw/d, based on ↑ corneal opacity (lactation) , ↓ BW (gestation & lactation; ↓ 5-7%) , ↓ FC (lactation; ↓ 8-12%); food spillage **Developmental** NOAEL = not established LOAEL = 0.8 mg/kg bw/d, based on ↓ post-weaning body weights, ↓ auditory startle amplitude (PND 60), ↓ terminal body weight (PND 75 males), ↓ absolute brain weight (PND 75 males; 2° to body weight effects), ↓ brain morphometrics (PND 75; frontal & parietal cortical thickness, cerebellum height - no dose-response)	1307497
Reverse gene mutation assay	*Salmonella typhimurium* & *Escherichia coli*	Negative	1328194
In vitro mammalian cell assay (HRPT)	Chinese Hamster ovary	Negative	1333986
In vitro mammalian clastogenicity	Human lymphocytes	Negative	1342335
In vivo mammalian cytogenetics (mouse micronucleus)	Mouse	Negative	1344703
Unscheduled DNA synthesis test	Rat hepatocytes	Negative	1345117

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Metabolism	Rat	**Absorption** AE 0172747 was determined to be quickly absorbed (94-96% in males and females at low and high doses) when administered in PEG 200, widely distributed amongst the tissues and effectively eliminated. The pharmacokinetics varied depending on the location of the label. When labelled on the phenyl ring, T_{max} was longer in males than females and there was little difference in elimination half-lives. When labelled on the cyclohexyl ring, T_{max} was longer in the females and their terminal elimination half-lives were 20 hours longer in low dose females than males compared to equivalent times in the high dose animals. Overall T_{max} values were also longer in the cyclohexyl ring-labelled AE 0172747 than the phenyl-labelled ring. C_{max} values indicated oversaturation of the absorption phase in phenyl ring-labelled AE 0172747 but not in cyclohexyl ring-labelled AE 0172747. There were not enough doses examined to determine whether the lack of saturation in absorption was related to the location of the label or the differences between the actual doses administered in the cyclohexyl (873.4 and 883.3 mg/kg bw/d for males and females) and phenyl studies (950.799 and 857.969 mg/kg bw/d for males and females respectively). In both the phenyl and cyclohexyl-labelled formulations, there was little sex difference in systemic exposure as measured by the area under the curve. **Distribution** The target organs were the liver and kidneys at low doses and the skin, liver and kidneys at high doses. Concentrations increased in the cardiac blood, intestines and contents, carcass, cardiac plasma, lungs and stomach and contents with increasing doses. Only between 3-4% of the administered dose was recovered in the tissues of animals administered 5 mg/kg bw. There is no evidence of bioaccumulation. **Excretion** Initial elimination was rapid, while terminal elimination was moderate. There were large sex differences in the metabolism and excretion of the administered compound. Males excreted more of the compound in the faeces at both low and high doses, however the proportion excreted in the urine increased proportional to the dose. In females, the majority of the compound was excreted in the urine at both low and high doses and there was less of a proportional increase excreted in the faeces as the dose increased. Oversaturation of the elimination/biotransformation pathways occurred at the high dose.	

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
		Metabolism The primary metabolic pathway was oxidation with the addition of hydroxyl groups on either or both rings in the molecule. Males tended to excrete more of the hydroxylated AE 0172747, especially at low doses, while females excreted more of the parent compound. As the dose increased, the pattern of metabolism and excretion became more similar between the sexes, but was never identical. Males excreted the AE 0172747 through the hepatobillary system.	

[a] Effects observed in males as well as females unless otherwise reported

Table 6 Toxicity Profile of Metabolites of Tembotrione

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
AE 0456148			
28-day dermal	Rat	Systemic toxicity: NOAEL: not established LOAEL: 250 mg/kg bw/d based on increased incidence of follicular cell hypertrophy and colloid alteration in the thyroid of males and females, and slight to moderate degenerative changes/increase of apoptotic bodies of exocrine acinar tissue in the pancreas accompanied by inflammatory infiltrates in both sexes Dermal irritation: NOAEL: 1000 mg/kg bw/d LOAEL: N/A	1359893
28-day dermal	Rat	Systemic toxicity: NOAEL: ♂ = not established; ♀ = 50 mg/kg bw/d LOAEL: ♂ = 50 mg/kg bw/d based on degeneration and apoptosis in the exocrine acinar tissue of the pancreas and increased incidence of colloid alternation in the thyroid; ♀ = 250 mg/kg bw/d based on degeneration and apoptosis in the exocrine acinar tissue of the pancreas and increased incidence of colloid alteration in the thyroid Dermal irritation: NOAEL: 1000 mg/kg bw/d LOAEL: N/A	1361240

[a] Effects observed in males as well as females unless otherwise reported

Table 7 Toxicology Endpoints for Use in Health Risk Assessment for Tembotrione

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	UF/SF^1 or Target MOE^2
Acute dietary, females aged 13+	NOAEL = 0.8 mg/kg bw/d	DNT	↓ BW (↓ 4-6%; PND 28-70), ↓ auditory startle amplitude (PND 60; ↓ overall 25-50%); ♂ only at 0.8 mg/kg bw/day, ↓ terminal BW PND 75 ♂ (↓ 7-8%), ↓ abs brain wt & ↑ rel brain wt (PND 75 ♂; 2° to BW effects), ↓ brain morphometrics on PND 75 (frontal & parietal cortical thickness (↓ 5-10%); cerebellum height (↓ 5-11%); no dose-response) in pups	1000
	ARfD = 0.0008 mg/kg bw/d			
Chronic Dietary	NOAEL = 0.04 mg/kg bw/d	Male Rat Chronic study	increased polyarteritis nodosa, increased cholesterol, increased sinusoid dilatation, fibrosis, extramedullary haematopoeisis, haemorrhages and hypertrophy of the liver, obviously large size, irregular surface, pale and/or mottled colouration, increased debris and transitional cell hyperplasia of the kidney and increased urinary ketones and proteins, keratitis of the eye, dilatation of the lacrimal gland, enlarged spleens, epithelial hyperplasia of the stomach and cystic hyperplasia and colloid alteration in the thyroid in males	100
	ADI = 0.0004 mg/kg bw/d			
Short-term Dermal	NOAEL = 0.8 mg/kg bw/d	DNT		1000
Intermediate-term Dermal	NOAEL = 0.8 mg/kg bw/d	DNT		1000

[1] Dietary scenerios

[2] Exposure scenerios

Table 8 Nature of Residues

NATURE OF THE RESIDUE IN CORN			**PMRA ##** 1270572, 1270568
Radiolabel Position	[Cyclohexyl-UL-^{14}C]-AE 0174727 or [Phenyl-UL-^{14}C]-AE 0174727		
Test Site	Outdoor, in stainless steel containers.		
Treatment	Foliar treatment		
Rate	[Cyclohexyl-UL-^{14}C]-AE 0174727 (171 g a.i./ha), [Phenyl-UL-^{14}C]-AE 0174727 (203 g a.i./ha); applied with safener (1:1, w:w)		
End-use product	formulated as an oil-based SC formulation		
Preharvest interval	84-89 days (forage), 113-124 days (stover, grain)		
Matrix	PHI (days)	[Cyclohexyl-UL-^{14}C]-AE 0174727	[Phenyl-UL-^{14}C]-AE 0174727
		TRR (ppm)	TRR (ppm)
Immature plant	0	13.721	53.747
Immature plant	14	0.715	3.785
Immature plant	29	0.120	n/a

Immature plant	49	0.019	0.053
Forage	84-89	0.035	0.066
Stover (including cobs)	113-124	0.025	0.124
Grain	113-124	0.003	0.029

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Cyclohexyl-UL-^{14}C]-AE 0174727**	**[Phenyl-UL-^{14}C]-AE 0174727**	**[Cyclohexyl-UL-^{14}C]-AE 0174727**	**[Phenyl-UL-^{14}C]-AE 0174727**
Immature plant (29 DAT)	AE 1417268 (M5)	not analyzed (n/a)	tembotrione	n/a
Immature plant (49 DAT)	AE 1417268 (M5)	AE 1417268 (M5), AE 0456148 (M6)	--	AE 1392936 (M2)
Forage (84-89 DAT)	AE 1417268 (M5)	AE 0456148 (M6), AE 1392936 (M2)	--	AE 1417268 (M5)
Stover (113 DAT)	AE 1417268 (M5)	AE 0456148 (M6), AE 1392936 (M2)	--	AE 1417268 (M5)
Grain (113 DAT)	n/a	AE 0456148 (M6)	n/a	AE 1417268 (M5)

Tembotrione is metabolized in corn by hydroxylation of the cyclohexyl moiety to form the monohydroxy (M10) and dihydroxy (M5) metabolites, followed by cleavage to the benzoic acid derivatiove (M6). The metabolite M2 is formed by subsequent cleavage of the trifluoroethoxy ether bond of M6.
The TRR in [cyclohexyl-UL-^{14}C]AE 0172747 treated corn grain was too low to be analyzed.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Swiss chard, turnip, wheat		**PMRA** #1270608	
Radiolabel Position		**[Phenyl-UL-^{14}C]-AE 0174727**	
Test site		greenhouse	
Formulation used for trial		The radiolabeled test substance was combined with nonlabeled tembotrione and diluted with ACN	
Application rate and timing		Soil was treated at 212 g a.i./ha. Rotational crops Swiss chard, turnip and wheat were planted at 90 days after soil treatment (PBI).	
Metabolites Identified		**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Matrix	**PBI (days)**	**[Phenyl-UL-^{14}C]-AE 0174727**	**[Phenyl-UL-^{14}C]-AE 0174727**
Swiss chard	90	AE 0456148 (M6)	--
Turnip tops	90	AE 0456148 (M6)	--
Turnip roots	90	AE 0456148 (M6)	AE 1392936 (M2)
Wheat forage	90	AE 0456148 (M6), AE 1392936 (M2)	--
Wheat hay	90	AE 0456148 (M6), AE 1392936 (M2)	--
Wheat straw	90	AE 0456148 (M6), AE 1392936 (M2)	--
Wheat grain	90	AE 0456148 (M6)	--

The metabolic profile of tembotrione in confined rotational crops involves cleavage of the complete cyclohexyl moiety from the parent compound leaving the benzoic acid moiety of the molecule, AE 0456148, and to a lesser extent subsequent cleavage of the ether bond to form AE 1392936.

NATURE OF THE RESIDUE IN LAYING HEN			**PMRA #** 1270574, 1270569	
Laying hens were dosed orally once daily for 14 consecutive days with either [cyclohexyl-UL-^{14}C]-AE 0172747 or [phenyl-UL-^{14}C]-AE 0172747 at 1 ppm and 10 ppm in the diet. Hens were sacrificed ~ 24 hrs after the final dose.				
Matrices	**% of Administered Dose**			
	[Cyclohexyl-UL-^{14}C]-AE 0172747		**[Phenyl-UL-^{14}C]-AE 0172747**	
	1 ppm dose	**10 ppm dose**	**1 ppm dose**	**10 ppm dose**
Excreta	91.85	95.86	92.18	88.93
Muscle	0.006	0.003	0.099	0.053
Fat	<0.001	<0.001	0.003	0.002
Skin with attached fat	0.002	0.001	0.032	0.026
Liver	0.219	0.022	2.683	0.441
Egg, white	0.015	0.012	0.005	0.006
Egg, yolk	0.052	0.041	0.068	0.066
Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[Cyclohexyl-UL-^{14}C]-AE 0172747**	**[Phenyl-UL-^{14}C]-AE 0172747**	**[Cyclohexyl-UL-^{14}C]-AE 0172747**	**[Phenyl-UL-^{14}C]-AE 0172747**
Muscle	tembotrione	tembotrione	–	–
Fat	tembotrione	tembotrione	–	–
Liver	tembotrione	tembotrione	hydroxy metabolite	–
Skin with attached fat	tembotrione	tembotrione	–	–
Egg, white	tembotrione	tembotrione	–	–
Egg, yolk	tembotrione	tembotrione	–	–

NATURE OF THE RESIDUE IN LACTATING COW				**PMRA #** 1270576, 1270575, 1270573		
[Cyclohexyl-UL-^{14}C]-AE 0172747 or [phenyl-UL-^{14}C]-AE 0172747 was administered orally to two cows each, one at 1 ppm and one at 10 ppm in the diet for 7 consecutive days. In another study, [cyclohexyl-UL-^{14}C]-AE 1417268 (M5), a plant metabolite of tembotrione, was admininstered orally to a single cow at 10 ppm in the diet. In all studies, milk was collected twice daily, and tissues were collected at sacrifice, ~ 24 hours after the final dose.						
Matrices	**% of Administered Dose**					
	[Cyclohexyl-UL-^{14}C]-AE 0172747		**[Phenyl-UL-^{14}C]-AE 0172747**		**[Cyclohexyl-UL-^{14}C]-AE 1417268 (M5)**	
Urine and feces, cage wash	75.6–86.8		73.2–110.8		74.3	
Muscle	<0.001		<LOQ		<LOQ	
Fat	<0.001		<0.001		<LOQ	
Kidney	0.07–0.58		0.09–0.66		0.039	
Liver	1.54–15.9		1.56–11.7		0.61	
Milk	0.095–0.125		0.007–0.025		0.054	
Metabolites identified	**Major Metabolites (> 10% TRR)**			**Minor Metabolites (< 10% TRR)**		
Radiolabel Position	**[Cyclohexyl-UL-^{14}C]-AE 0172747**	**[Phenyl-UL-^{14}C]-AE 0172747**	**[Cyclohexyl-UL-^{14}C]-AE 1417268 (M5)**	**[Cyclohexyl-UL-^{14}C]-AE 0172747**	**[Phenyl-UL-^{14}C]-AE 0172747**	**[Cyclohexyl-UL-^{14}C]-AE 1417268 (M5)**
Fat	tembotrione	n/a	n/a	–	n/a	n/a
Muscle	tembotrione	n/a	n/a	–	n/a	n/a

Kidney	tembotrione	tembotrione	M5	–	–	–
Liver	tembotrione	tembotrione	M5	–	–	–
Milk	tembotrione	n/a	–	–	n/a	–

More than 73% of the administered dose was excreted.
No significant metabolism of AE 0172747 (tembotrione) was observed in ruminants as the unchanged parent molecule was the primary residue component identified in all milk and tissue samples.
The AE 1417268 (the dihydroxy metablolite, M5) metabolism study showed M5 also underwent minimal metabolism in ruminant.

STORAGE STABILITY | **PMRA** # 1270592, 1270593

Samples of mustard greens, turnip roots, yellow squash, corn (grain, forage, stover) spiked with tembotrione, M5, M2 and M6 at levels of 0.2 or 0.4 ppm were stored at ≤–10°C for a duration of 11-13 months. Tembotrione and the metabolites were analyzed by HPLC-MS/MS Method No. AE/03/01. The results show that residues of tembotrione, M6 and M2 are stable for 350 days and M5 is stable for 370 days in/on mustard greens, turnip roots and yellow squash. Residues of tembotrione, M6 and M2 are stable in corn matrices for 396 days. Residue of M5 were stable in corn forage and stover for 12 months; stable in corn grain for 6 months (78% recovery) but declined to 61% in corn grain after stored frozen for 317 days.

As samples in livestock metabolism studies and feeding study were analysed within 6 months and 1 month, respectively, of freezer storage, freezer storage stability study in animal matrices are not required.

CROP FIELD TRIALS - Field Corn | **PMRA#** 1270602

21 trials were conducted on field corn in zones 1 (1 trial), 2 (1 trial), 5 (18 trials), and 6 (1 trial) at a total trial rate of 180-195 g a.i./ha/season (~4.7× proposed GAP rate for Trilogy Herbicide).

Commodity (Field corn)	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm) Total residues of tembotrione (tembotrione + M5)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Corn grain	180-195	76-112	84	<0.02	<0.025	<0.023	0.02	0.02	–
Corn forage	180-195	44-53	84	<0.032	<0.375	<0.342	0.140	0.152	0.081
Corn stover	180-195	76-112	84	<0.02	<0.450	<0.428	0.049	0.083	0.097

At maturity, parent compound tembotrion was not detected in any of the 84 grain samples (<LOD, 0.001 ppm); M5 was <LOQ (0.01ppm) in all the grain samples except 2 samples which had M5 at 0.012 ppm and 0.015 ppm.
For the calculation of the median, mean and Std, LOQ (0.01 ppm/analyte) was used for residues reported below the LOQ.

CROP FIELD TRIALS - Sweet Corn | **PMRA#** 1270601

12 trials were conducted on sweet corn in zones 1 (2 trials), 2 (1 trial), 3 (1 trail), 5 (5 trials), 10 (1 trial), 11 (1 trial), and 12 (1 trial) at a total trial rate of 182-190 g a.i./ha/season (~1× US GAP).

Commodity (Sweet corn)	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm) Total residues of tembotrione (tembotrione + M5)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
K+CWHR	182-190	44-46	48	<0.02	<0.035	<0.028	0.02	0.02	–
forage	182-190	44-46	48	<0.02	<0.911	<0.751	0.220	0.258	0.192
stover	182-190	46-95	48	<0.02	<0.854	<0.664	0.039	0.108	0.158

In the sweet corn kernels plus cob with husk removed (K+CWHR), parent compound tembotrion was not detected in any of the 48 grain samples (<LOD, 0.001 ppm); M5 was <LOQ (0.01ppm) in all the grain samples except 1 samples which had M5 at 0.025 ppm.
For the calculation of the median, mean and Std, LOQ (0.01 ppm/analyte) was used for residues reported below the LOQ.

CROP FIELD TRIALS - Pop Corn | **PMRA#** 1270600

4 trials were conducted on pop corn in zones 5 (3 trials) and 8 (1 trial) at a total trial rate of 184-193 g a.i./ha/season (1× US GAP).

Commodity (Pop corn)	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm) Total residues of tembotrione (tembotrione + M5)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
grain	184-193	72-93	16	<0.02	<0.02	<0.02	0.02	0.02	–
stover	184-193	72-93	16	<0.02	<0.202	<0.192	0.028	0.66	0.069

FIELD ROTATIONAL CROP TRIALS - | **PMRA #** 1270610, 1270609

Tembotrione was applied to the primary crop, corn, at a seasonal rate of 184–195 g a.i./ha. Once the primary crops were harvested, rotational crops mustard greens, turnips, summer squash and winter wheat were planted at approximately 90-120 days PBI. No residues of tembotrione, M5, M6 and M2 were greater than the LOQ (0.01 ppm/analyte) in winter wheat (forage, hay, straw & grain), mustard greens, turnips (tops & roots), and summer squash at all PBIs.

PROCESSED FOOD AND FEED – Field corn | **PMRA #** 1270606

Test Site	1 trial conducted in IL
Treatment	foliar treatment
Rate	457 g a.i./ha/application, 2 applications for a total of 914 g a.i./ha.
End-use product	AE 0172747 02 SC52 A1
Preharvest interval	71 days
Processed Commodity	refined oil, flour, grits, meal, starch

	Residues of Tembotrione (sum of parent + M5 + M6 + M2)	Processing Factor
RAC	0.370 ppm	–
Refined oil	0.003 ppm	0.01×
Flour	0.323 ppm	0.87×
Grits	0.363 ppm	0.98×
Meal	0.415 ppm	1.12×
Starch	0.017 ppm	0.05×

LIVSESTOCK FEEDING – Dairy cattle fed with tembotrione | **PMRA #** 1270594

Three treatment groups of three dairy cows each were dosed with tembotrione at target dose rate of 3.2 ppm, 9.6 ppm and 32 ppm in feed for 29 consecutive days. Milk was collected twice daily. After 29 days of dosing, cows were sacrificed and samples of kidney, liver, muscle and fat were collected within 8 hours of the last dosing. Milk and tissue samples were analysed for residue of parent tembotrione.

For residues below the LOQ or LOD, LOQ (0.01ppm) was used for the calculation of median, mean and standard deviation.

Matrix	Feeding Level (ppm/d)	n	LOD	Min	Max	Median	Mean	Standard Deviation
Liver	3.2	3	0.0024	2.0	2.89	2.46	2.45	0.448
Kidney		3	0.0014	0.394	0.454	0.446	0.431	0.033
Muscle		3	0.002	<0.010	<0.010	0.010	0.010	–
Fat		3	0.0011	<0.010	<0.010	0.010	0.010	–

Liver	9.6	3	0.0024	1.4	2.96	2.64	2.33	0.825
Kidney		3	0.0014	0.213	0.486	0.477	0.392	0.155
Muscle		3	0.002	<0.010	<0.010	0.010	0.010	–
Fat		3	0.0011	<0.010	<0.010	0.010	0.010	–
Liver	32	3	0.0024	2.93	3.35	3.08	3.12	0.21
Kidney		3	0.0014	0.788	1.37	0.856	1.00	0.317
Muscle		3	0.002	<0.010	0.014	0.010	0.011	0.012
Fat		3	0.0011	<0.010	0.025	0.010	0.015	0.009
Milk	all dose levels	11-33	0.0019	<0.010	<0.010	0.010	0.010	–

LIVSESTOCK FEEDING – Dairy cattle fed with M5 (AE 1417268) **PMRA #** 1270596

Four treatment groups of three dairy cows each were dosed with M5 at target dose rate of 0.05 ppm, 0.5 ppm, 1.5 ppm and 5.0 ppm in feed for 28-31 consecutive days. Milk was collected twice daily. After the last days of dosing, cows were sacrificed; the cows for the depuration study were sacrificed 7, 14 and 28 days after the final dose. Milk and tissue samples (kidney, liver, muscle and fat) were analysed for residue of M5.

For residues below the LOQ or LOD, LOQ (0.01ppm for tissues, 0.002 ppm for milk) was used for the calculation of median, mean and standard deviation.

Matrix	Feeding Level (ppm/d)	n	LOD	Min	Max	Median	Mean	Standard Deviation
Liver	0.05	3	0.002	<0.010	<0.010	0.010	0.010	–
Kidney		3	0.002	<0.010	<0.010	0.010	0.010	–
Liver	0.5	3	0.002	0.029	0.036	0.030	0.032	0.004
Kidney		3	0.002	0.013	0.017	0.015	0.015	0.002
Liver	1.5	3	0.002	0.084	0.163	0.150	0.132	0.042
Kidney		3	0.002	0.037	0.049	0.040	0.042	0.006
Liver	5	3	0.002	0.305	0.386	0.333	0.341	0.041
Kidney		3	0.002	0.122	0.165	0.139	0.142	0.022
Muscle	all dose levels	3	0.002	<0.010	<0.010	0.010	0.010	--
Fat		3	0.002	<0.010	<0.010	0.010	0.010	--
Milk		24-33	0.001	<0.002	<0.002	0.002	0.002	--

The estimated maximum reasonable balanced diet (MRBD) were calculated to be 0.16 ppm for beef cattle, 0.43 ppm for dairy cattle, 0.02 ppm for poultry, and 0.02 ppm for swine.

M5 is the major metabolite in corn plant. The MRBDs for M5, using field trial residue data, were calculated to be 0.15 ppm for beef cattle, 0.42 ppm for dairy cattle.

To be conservative, anticipated residues calculated in dairy cattle are used to set the MRLs. MRBD for Tembotrione = MRBD (0.43 ppm) - M5 MRBD (0.42 ppm) = 0.01 ppm.

Anticipated Residue is calculated by MRBD × residue/feed ratio or transfer coefficients.

For swine, at MRBD of 0.02 ppm for tembotrione and M5, no residues of tembotrione and M5 are expected to be detected in swine commodities.

Commodity	**Feeding level (ppm)**		**Maximum Residues (ppm)**		**MRBD (ppm)**			**Anticipated Residue (tembotrione + M5) (ppm)**	
					Beef/Dairy		**Hog**		
	tembotrione	**M5**	**tembotrione**	**M5**	**tembotrione**	**M5**	**tembotrione + M5**	**Beef/Dairy**	**Hog**
Liver	3.2	1.5	2.89	0.163	0.01	0.42	0.02	0.038	<0.02
Kidney			0.454	0.05				0.013	<0.02
Fat	32	5	0.025	<0.01				<0.0008	<0.02
Muscle			0.014	<0.01				<0.0008	<0.02
Milk			<0.01	<0.002				<0.0002	–

LIVESTOCK FEEDING – Laying hens	**PMRA #** 1270599

Three treatment groups of 12 laying hens each were dosed with tembotrione at target dose rate of 0.2 ppm, 0.6 ppm and 2.0 ppm in feed for 29 consecutive days. Eggs were collected twice daily. After 29 days of dosing, hens were sacrificed within 3-5 hours of the final dose, and samples of liver, skin, muscle and fat were collected. Egg and tissue samples were analysed for residue of parent tembotrione using Method AE-004-A04-01. The LOQ is 0.01 ppm for eggs and tissues. For residues below the LOQ or LOD, LOQ (0.01ppm) was used for the calculation of median, mean and standard deviation.

Matrix	**Feeding Level (ppm/d)**	**Residue Levels (ppm)**						
		n	**LOD**	**Min**	**Max**	**Median**	**Mean**	**Standard Deviation**
Liver	0.2	3	0.0025	0.326	0.504	0.421	0.417	0.089
Skin		3	0.0031	<0.010	<0.010	0.010	0.010	–
Fat		3	0.0031	<0.010	<0.010	0.010	0.010	–
Muscle		3	0.0026	<0.010	<0.010	0.010	0.010	–
Liver	0.6	3	0.0025	0.568	0.618	0.583	0.590	0.026
Skin		3	0.0031	<0.010	0.013	0.011	0.010	0.004
Fat		3	0.0031	<0.010	<0.010	0.010	0.010	–
Muscle		3	0.0026	<0.010	<0.010	0.010	0.010	–
Liver	2	3	0.0025	0.584	0.702	0.666	0.651	0.060
Skin		3	0.0031	0.040	0058	0.052	0.050	0.009
Fat		3	0.0031	0.019	0.034	0.023	0.025	0.008
Muscle		3	0.0026	0.016	0.020	0.018	0.018	0.002
Egg		33	0.0018	<00010	<0.010	0.010	0.0100	–

Using recommended MRLs, the estimated maximum reasonably balanced diet (MRBD) was calculated to be 0.02 ppm for poultry. No separate poultry feeding study with M5 was conducted.

Based on poultry feeding study conducted with tembotrione, at MRBD of 0.02 ppm, no residues are expected to be detected on poultry fat, muscle and eggs.

Commodity	Feeding level (ppm)	Maximum residues (ppm)	MRBD (ppm)	Anticipated residue (ppm)
Liver	0.2	0.504	0.02	0.050
Fat	2	0.034		0.0003
Muscle		0.020		0.0002
Egg		<0.010		<0.0001

Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (corn)** **Rotational crops**	Tembotrione and M5 Tembotrione
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	Tembotrione and M5 Tembotrione
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops cannot be determined, because only corn was investigated.
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	Tembotrione and M5
RESIDUE DEFINITION FOR RISK ASSESSMENT	Tembotrione and M5
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	The profile is similar in animals investigated. No significant metabolism of tembotrione was observed in livestock. The parent compound was the primary residue component in ruminant and poultry
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND WATER (for the use Trilogy Herbicide)			
Refined chronic non-cancer dietary risk **ADI = 0.0004 mg/kg bw** **Estimated chronic drinking water concentration = 4.8 μg/L (3 years use)** Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates which resulted from the use of tembotrion (Capreno Herbicide) on field corn in Canada, including sweet corn and popcorn imported to Canada. The assessment used the field trial median residue data and assumed 100% crop treated.	**POPULATION**	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
	All infants < 1 year	13.2	96.1
	Children 1–2 years	22.8	60.4
	Children 3 to 5 years	25.5	60.7
	Children 6–12 years	19.3	43.5
	Youth 13–19 years	14.4	32.7
	Adults 20–49 years	8.6	32.2
	Adults 50+ years	5.0	29.9
	Females 13 to 49 yrs	8.6	32.1
	Total population	10.7	36.0

Refined acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 4.8 µg/L (3 years use)** **ARfD = 0.0008 mg/kg bw** The assessment used the field trial HAFT residue data for field corn, popcorn, max. residue for sweet corn, and assumed 100% crop treated.	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
	All infants < 1 year	43.1	136.2
	Children 1–2 years	38.4	75.4
	Children 3 to 5 years	38.1	70.5
	Children 6–12 years	28.9	50.5
	Youth 13–19 years	23.1	38.1
	Adults 20–49 years	15.1	36.0
	Adults 50+ years	9.6	30.3
	Females 13 to 49 yrs	15.8	36.1
	Total population	20.5	43.4

Table 10 List of Synonyms for Tembotrione Transformation Products

Transformation Product Number	Code Number assigned by Applicant	CAS Name	Comments
M1	AE 0968400	2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]phenol	
M2	AE 1392936	2-chloro-3-(hydroxymethyl)-4-(methylsulfonyl)benzoic acid	
M3	AE 0941989	3,4-dihydro-6-(methylsulfonyl)-5-[(2,2,2-trifluoroethoxy)methyl]-1Hxanthene-1,9(2H)-dione	
M4	AE 1275213	Pentanedioic acid	Glutaric acid (IUPAC name)
M6	AE 0456148	2-chloro-4-(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl]benzoic acid	
M7	AE 1124336	2-chloro-1-methoxy-4(methylsulfonyl)-3-[(2,2,2-trifluoroethoxy)methyl] benzene	

Table 11 Fate and Behaviour in the Terrestrial Environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	**TGAI:** tembotrione	Half-life at 25°C pH 5: stable pH 7: stable pH 9: stable	Not expected to be an important route of transformation
Phototransformation on soil	**TGAI:** tembotrione	Half-life irradiated: 8.2 days dark: 117.5 days	Not expected to be an important route of transformation
Phototransformation in air	**TGAI:** tembotrione	Data not required	Not volatile
Biotransformation			
Biotransformation in aerobic soil	**TGAI:** tembotrione	DT_{50}: 4.5, 5.7, 6.6, 14.6, 127 and 194 days major biotransformation products: M6, M1, M2, M3, CO_2 minor biotransformation products: M7, M1	Non-persistent to persistent
	Transformation Product: **M3** (0941989)	DT_{50}: <2 days	Non-persistent
	Transformation Product: **M2** (1392936)	DT_{50}: 7-21 days	Non-persistent to slightly persistent
Biotransformation in anaerobic soil	**TGAI:** tembotrione	DT_{50}: water: > 120 days (testtermination) sediment: > 120 days (test termination) total system: > 120 days (test termination) major and minor biotransformation products: none during anaerobic phase of test	Persistent

Property	Test substance	Value	Comments
Mobility			
Adsorption	**TGAI:** tembotrione	K_{oc}: 23.0–92.7	Very high mobility expected
	Transformation Product: **M2** (1392936)	Freundlich Koc : 0.0-18.1 (1/n ≅ 1, or not reported)	Very high mobility expected
	Transformation Product: **M7** (1124336)	K_{oc}: 205-372	Moderated mobility expected
	Transformation Product: **M1** (0968400)	K_{oc}: 21-101	High to very high mobility expected
	Transformation Product: **M3** (0941989)	Freundlich K_{oc}: 400-1743 (1/n ≅ 1)	Low to moderate mobility expected
	Transformation Product: **M6** (0456148)	Freundlich K_{oc}: 0.07-3.65 (1/n ≅ 1, except in two cases)	Very high mobility expected
Terrestrial Field Dissipation			
Field dissipation (New York)	**EP :** AE 0172747 02 SC 52 Herbicide	DT_{50}: 11.4 days	Non-persistent

Table 12 Fate and Behaviour in the Aquatic Environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	**TGAI:** tembotrione	half-life at 25°C pH 5: stable pH 7: stable pH 9: stable	Not expected to be an important route of transformation
Phototransformation in water	**TGAI:** tembotrione	half-life irradiated: 56 days dark: stable	Not expected to be an important route of transformation.
Biotransformation			
Biotransformation in aerobic water systems	**TGAI:** tembotrione	Observed DT_{50}'s – combined labels: water: 12-64 days sediment: 41-139 days total system: 64-222 days Major transformation product: M6 Minor transformation product: M1	water: slightly persistent sediment: slightly to moderately persistent total system: moderately persistent to persistent
Biotransformation in aerobic water systems	**TGAI:** tembotrione	Observed DT_{50}'s – combined labels: water: 14-30 days sediment: >365 days total system: >365 days Major transformation product: none Minor transformation product: M6	water: slightly persistent sediment: persistent total system: persistent

Table 13 Toxicity to Non-Target Terrestrial Species

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	**TGAI:** tembotrione	LD_{50}:>100 mg/kg NOEL (slow reaction): 18 mg/kg NOEL (body weight change): 56 mg/kg NOEL (mortality): 100 mg/kg	No classification
	Acute	Transformation Product: **M1** (AE 0968400)	LD_{50}: > 1000 mg/kg NOEL (slow reaction): 100 mg/kg NOEL (body weight change): 125 mg/kg NOEL (mortality): 1000 mg/kg	No classification
	Acute	Transformation Product: **M2** (AE 1392936)	LD_{50}: > 1000 mg/kg NOEL (slow reaction): 1000 mg/kg NOEL (body weight change): 1000 mg/kg NOEL (mortality): 1000 mg/kg	No classification
	Acute	Transformation Product: **M3** (AE 0941989)	LD_{50}: > 1000 mg/kg NOEL (slow reaction): 1000 mg/kg NOEL (body weight change): 1000 mg/kg NOEL (mortality): 1000 mg/kg	No classification
	Acute	Transformation Product: **M6** (AE 0456148)	LD_{50}: > 1000 mg/kg NOEL (slow reaction): 1000 mg/kg NOEL (body weight change): 1000 mg/kg NOEL (mortality): 1000 mg/kg	No classification
	Acute	Transformation Product: **M7** (AE 1124336)	LD_{50}: > 1000 mg/kg NOEL (slow reaction): 1000 mg/kg NOEL (body weight change): 1000 mg/kg NOEL (mortality): 1000 mg/kg	No classification

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Honey Bee	Contact	**TGAI:** tembotrione	LD_{50}: > 100 g a.i./bee NOEL (mortality): 10 g a.i./bee	Relatively non-toxic according to Atkins (1981)
	Contact	**EP:** AE 0172747 02 SC 52 Herbicide	LD_{50}: > 130.4 g a.i./bee (> 384.6 g end use product/bee) NOEL (mortality): 130.4 g a.i./bee	Relatively non-toxic according to Atkins (1981)
	Oral	**TGAI:** tembotrione	LD_{50}:> 92.8 g a.i./bee NOEL (mortaliy and sub-lethal effects): 92.8 g a.i./bee	Relatively non-toxic according to Atkins (1981)
	Oral	**EP:** AE 0172747 02 SC 52 Herbicide	LD_{50}:> 153.4 g a.i./bee NOEL (mortality and "damaged" bees): 84.8 g a.i./bee	Relatively non-toxic according to Atkins (1981)
Birds				
Bobwhite quail	Acute oral	**TGAI:** tembotrione	LD_{50}: > 2250 mg ai/kg bw NOEL (ruffled appearance, lethargy): 486 mg ai/kg bw	Practically non-toxic
	Acute dietary	**TGAI:** tembotrione	LD_{50}: >5790 mg ai/kg diet NOEL (body weight gain): 1890 mg ai/kg diet	Practically non-toxic
	Reproduction	**TGAI:** tembotrione	LOEL: 250 mg ai/kg diet NOEL (viable embryos/eggs set): 65.3 mg ai/kg diet	No classification

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Mallard duck	Acute oral	**TGAI:** tembotrione	LD_{50}: > 292 mg ai/kg bw NOEL (regurgitation and "sublethal signs"): 105 mg ai/kg bw NOEC (male body weight): 1000 mg ai/kg bw	Moderately toxic
	Acute dietary	**TGAI:** tembotrione	LD_{50}: > 5620 mg ai/kg diet NOEL (body weight gain): <580 mg ai/kg diet (lowest treatment level was affected) NOEL (food consumption): 1000 mg ai/kg NOEL (mortality and clinical signs): 5620 mg ai/kg diet	Practically non-toxic
	Reproduction	**TGAI:** tembotrione	Study 1. LOEL: 65.3 mg ai/kg diet (lowest concentration tested) NOEL: < 65.3 mg ai/kg diet Study 2. LOEL: 22.4 mg ai/kg diet (lowest concentration tested) NOEL: < 22.4 mg ai/kg diet	No classification
Mammals				
Rat	Acute oral	**TGAI:** tembotrione	LD_{50}: > 2000 mg ai/kg bw NOEL (mortality): 2000 mg/kg bw NOEL (yellow staining in urogenital area): 630 mg/kg bw	No classification
	Acute oral	**EP:** AE 0172747 02 SC 52 Herbicide	LD_{50}♀: 577.5 mg ai/kg bw NOEL (mortality): 181.5 mg ai/kg bw NOEL (piloerection,hypoactivity, and/or reduced faecal output on day 1): 181.5 mg ai/kg bw	No classification
	Dietary (90 day)	**TGAI:** tembotrione	NOEL♂/♀ (sublethal effects in multiple organs): 0.07/0.08 mg/kg bw	No classification
	Reproduction (2-generation)	**TGAI:** tembotrione	LOEL ♂/♀ (eye pathology): 1.3/1.6 mg/kg bw	No classification
Mouse	Dietary (90 day)	**TGAI:** tembotrione	NOEL♂/♀ (sublethal effects in multiple organs): 64/76 mg/kg bw	No classification
Rabbit	Developmental (Reproduction)	**TGAI:** tembotrione	LOEL ♀ (decreased faecal output and food consumption): 10 mg/kg bw	No classification

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Vascular plants				
Vascular Plant	Seedling emergence	**EP:** AE 0172747 02 SC 52 Herbicide	most sensitive onocot – dry weight NOEC (onion): 0.012 kg ai/ha EC$_{25}$ (onion): > 0.031 kg ai/ha most sensitive dicot – dry weight NOEC lettuce): 0.00039 kg ai/ha EC25 (lettuce): 0.00044 kg ai/ha	No classification
	Vegetative vigour	**EP:** AE 0172747 02 SC 52 Herbicide	most sensitive monocot – dry weight NOEC (onion): 0.0029 kg ai/ha EC$_{25}$ (onion): > 0.0056 kg ai/ha most sensitive dicot – dry weight NOEC (tomato): 0.00039 kg ai/ha EC$_{25}$ (tomato): 0.00044 kg ai/ha	No classification

[a] Atkins et al. (1981) for bees, and US EPA classification scheme for others, where applicable.

Table 14 Toxicity to Non-Target Aquatic Species

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Freshwater Invertebrates				
Daphnia magna	48-hour acute	**TGAI:** tembotrione	EC$_{50}$: 48.9 mg ai/L NOEC : 15.68 mg ai/L (Immobilization)	Slightly toxic
	48-hour acute	Transformation product **M6** (AE 0456148)	EC$_{50}$: > 115 mg ai/L NOEC : 115 mg ai/L (Immobilization) (115 mg ai/L is the highest test concentration)	Practically non-toxic
	48-hour acute	**EP:** AE 0172747 02 SC 52 Herbicide	EC$_{50}$: 11.6 mg ai/L NOEC: 4.11 mg ai/L (Immobilization)	Slightly toxic
	21-day chronic	**TGAI:** tembotrione	EC$_{50}$: > 10.19 mg ai/L (immobilization) NOEC: 5.10 mg ai/L (reduction in length of surviving parents)	No classification
	21-day chronic	Transformation product **M6** (AE 0456148)	EC$_{50}$: > 113 mg metabolite/L NOEC: 113 mg metabolite/L (Immobilization) (113 mg metabolite/L is the highest test concentration)	No classification

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Chironomids	28-day chronic	**TGAI:** tembotrione	NOEC (emergence): 4.0 mg as /L NOEC (development rate): > 32 mg as/L (the highest test concentration	No classification
Freshwater Fish				
Rainbow trout	96-hour acute	**TGAI:** tembotrione	LC$_{50}$: > 101mg ai/L (only concentration tested - limit test) NOEC: 101 mg ai/L (mortality and sublethal effects)	Slightly toxic
	96-hour acute	Transformation product **M6** (AE 0456148)	LC$_{50}$: > 105mg metabolite/L (only concentration tested - limit test) NOEC: 105 mg metabolite/L (mortality and sublethal effects)	Slightly toxic
	96-hour acute	**EP:** AE 0172747 02 SC 52 Herbicide	LC$_{50}$: 1.83 mg ai/L NOEC (behavioural effects): < 0.127 mg ai/L, the lowest concentration tested NOEC (mortality): 1.05 mg ai /L	Moderately toxic
Bluegill sunfish	96-hour acute	**TGAI:** tembotrione	LC$_{50}$: > 100 mg ai/L NOEC: 100 mg ai/L (mortality and sublethal effects) (100mg ai/L was the only treatment)	Practically non- toxic
Fathead minnow	Chronic - 34- day	**TGAI:** tembotrione	NOEC Values: Time to hatch (day 3-5) 9.74mg a.i./L Hatching Success (day 5) 9.74mg a.i./L Fry survival (day 34) 0.0604 mg ai/L overall survival (day 34) 1.10 mg ai/L length 1.10 mg ai/L weight 1.10 mg ai/L morpholical and behavioural effects: 2.25 mg ai/L	No classification
Freshwater Algae				
Green alga	96-hour acute	**TGAI:** tembotrione	EC$_{50}$: 0.31 mg a.i./L (cell density) EC$_{50}$: 0.35 mg a.i./L (biomass) EC$_{50}$: 0.83 mg a.i./L (growth rate) NOEC: 0.02 mg a.i./L (all endpoints)	No classification
Green alga	72-hour acute	Transformation product **M6** (AE 0456148)	LC$_{50}$: > 103 mg ai/L NOEC: 103 mg ai/L (only concentration tested)	No classification

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Green alga	72-hour acute	**EP:** AE 0172747 02 SC 52 Herbicide	Cell density EC_{50}: 2.7 mg a.i./L NOEC: 0.773 mg a.i./L Growth rate EC50: 4.5 mg a.i./L NOEC: 1.92 mg ai/L	No classification
Diatom	120-hour	**TGAI:** tembotrione	Cell density EC_{50}: 11 mg a.i./L NOEC: 3.04 mg a.i./L Biomass EC_{50}: 9 mg a.i./L NOEC: 3.04 mg a.i./L Growth rate EC_{50}: 42 mg a.i./L NOEC: 5.34 mg ai/L	No classification
Freshwater Vascular Plants				
Lemna gibba G3	7-day	**TGAI:** tembotrione	EC_{50} (frond number): 5.2 µg ai/L EC_{50} (frond number growth rate): 8.9 µg ai/L EC_{50} (biomass growth rate): 14 µg ai/L EC_{50} (biomass dry weight): 6.7µg ai/L NOEC: 2.86 µg ai/L (All endpoints)	No classification
Lemna gibba G3	7-day	Transformation product **M6** (AE 0456148)	EC_{50} (frond number/growth rate, biomass growth rate/dry weight): > 105 mg ai/L NOEC 105 mg ai/L (all endpoints) (only concentration tested - limit test)	No classification
Marine Organisms				
Crustacean (mysid shrimp)	96-hour acute	**TGAI:** tembotrione	LC50: > 79 µg ai/L NOEC: 46 µg ai/L (abnormal behaviour)	Very highly toxic
	Chronic - 28-day	**TGAI:** tembotrione	NOEC: 5.7 µg ai/L (most sensitive endpoint - overall survival)	No classification
Mollusk (eastern oyster)	96-hour acute	**TGAI:** tembotrione	EC_{50}: 39 mg ai/L NOEC: 14 mg ai/L (shell growth)	Slightly toxic
Marine Fish - (sheepshead minnow)	96-hour acute	**TGAI:** tembotrione	LC_{50}: > 100 mg ai/L NOEC: 100 mg ai/L (highest concentration tested)	Practically non-toxic

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Marine diatom	96-hour acute	**TGAI:** tembotrione	Cell density EC50: 8.5 mg a.i./L NOEC: 2.6 mg a.i./L Biomass EC_{50}: 8.7 mg a.i./L NOEC: 2.6 mg a.i./L Growth rate EC_{50}: 24 mg a.i./L NOEC: 2.6 mg ai/L	No classification

[a] EPA classification scheme, where applicable

Table 15 Screening Level Risk Assessment for Terrestrial Non-target Species

Organism	Exposure: Test substance	Toxicity Endpoint Value	Converted Tox Endpoint Value	EEC	RQ Value	Level of Concern
Invertebrates						
Earthworm	Acute: **TGAI** tembotrione	LC_{50}:>100 mg ai/kg	$LC_{50} \div 2 =$ 50 mg ai/kg	0.0799 mg ai/kg	0.0016	Not Exceeded
	Acute: Transformation Product: **M1** (AE 0968400)	LC_{50}: > 1000 mg/kg	$LC_{50} \div 2 =$ 500 mg ai/kg	0.0799 mg ai/kg	0.001598	Not Exceeded
	Acute: Transformation Product: **M2** (AE 1392936)	LC_{50}: > 1000 mg/kg	$LC_{50} \div 2 =$ 500 mg ai/kg	0.0799 mg ai/kg	0.001598	Not Exceeded
	Acute: Transformation Product: **M3** (AE 0941989)	LC_{50}: > 1000 mg/kg	$LC_{50} \div 2 =$ 500 mg ai/kg	0.0799 mg ai/kg	0.001598	Not Exceeded
	Acute: Transformation Product: **M6** (AE 0456148)	LC_{50}: > 1000 mg/kg	$LC_{50} \div 2 =$ 500 mg ai/kg	0.0799 mg ai/kg	0.001598	Not Exceeded
	Acute: Transformation Product: **M7** (AE 1124336)	LC_{50}: > 1000 mg/kg	$LC_{50} \div 2 =$ 500 mg ai/kg	0.0799 mg ai/kg	0.001598	Not Exceeded

Organism	Exposure: Test substance	Toxicity Endpoint Value	Converted Tox Endpoint Value	EEC	RQ Value	Level of Concern
Honey Bee	Contact: **TGAI** tembotrione	NOEL (mortality): 10 g a.i./bee	10 g a.i./bee × 1.12 = 11.2 kg ai/ha	0.1682 kg ai/ha	0.015	Not Exceeded
	Contact: **EP** AE 0172747 02 SC 52 Herbicide	NOEL (mortality): 130.4 g a.i./bee	130.4 g a.i./bee × 1.12 = 146.048 kg ai/ha	0.1682 kg ai/ha	0.0015	Not Exceeded
	Oral: **TGAI** tembotrione	LD_{50}:> 92.8 g a.i./bee NOEL: 92.8 g a.i./bee	92.8 g ai/bee × 1.12 = 103.936 kg ai/ha	0.1682 kg ai/ha	0.0016	Not Exceeded
	Oral: **EP** AE 0172747 02 SC 52 Herbicide	NOEL (mortality and "damaged" bees): 84.8 g a.i./bee	84.8 g a.i./bee × 1.12 = 94.976 kg ai/ha	0.1682 kg ai/ha	0.0018	Not Exceeded
Birds						
Bobwhite quail	Acute oral: **TGAI** tembotrione	LD_{50}: > 2250 mg ai/kg bw	LD_{50} ÷ 10 = 225 mg ai/kg bw	3.12 mg ai/kg bw	0.0139	Not Exceeded
	Acute dietary: **TGAI** tembotrione	LC_{50}: >5790 mg ai/kg diet	LC_{50} ÷ 10 = 579 mg ai/kg diet	29.45 mg ai/kg diet	0.0509	Not Exceeded
	Reproduction: **TGAI** tembotrione	NOEC (viable embryos/eggs set): 65.3 mg ai/kg diet	NOEC 65.3 mg ai/kg diet (No conversion)	29.45 mg ai/kg diet	0.451	Not Exceeded
Mallard duck	Acute oral: **TGAI** tembotrione	LD_{50} not determined (no mortalities, and regurgitation occurred at all treatment levels) NOEL (regurgitation and "sublethal signs"): 105 mg ai/kg bw	No conversion was possible as LD_{50} could not be determined	0.3218 mg ai/kg bw	N/A	N/A
	Acute dietary: **TGAI** tembotrione	LC_{50}: > 5620 mg ai/kg diet	LC_{50} ÷ 10 = 562 mg ai/kg diet	5.69 mg ai/kg diet	0.01012	Not Exceeded
	Reproduction: **TGAI** tembotrione	NOEC: (viable embryos as a proportion of eggs set) 65.3 mg ai/kg diet	NOEC 65.3 mg ai/kg diet (No conversion)	5.69 mg ai/kg diet	0.08713	Not Exceeded

Organism	Exposure: Test substance	Toxicity Endpoint Value	Converted Tox Endpoint Value	EEC	RQ Value	Level of Concern
Small Mammals						
Rat	Acute oral: **TGAI** tembotrione	LD_{50}: > 2000 mg ai/kg bw	LD_{50} ÷ 10 = 200 mg ai/kg bw	14.55 mg ai/kg bw	0.07275	Not Exceeded
	Acute oral: **EP** AE 0172747 02 SC 52 Herbicide	LD_{50} ♀: 1750 mg ai/kg bw	LD_{50} × 33% for EP = 577.5 mg ai/kg bw LD_{50} ÷ 10 = 57.75 mg ai/kg bw	14.55 mg ai/kg bw	0.2519	Not Exceeded
	90-day dietary: **TGAI** tembotrione	NOEL: 0.07	NOEL: 0.07 (No conversion)	14.55 mg ai/kg bw	207.86	Exceeded
	Reproduction (2 generation): **TGAI** tembotrione	LOEL: 1.3	LOEL: 1.3 (No conversion)	14.55 mg ai/kg bw	11.19	Exceeded
Mouse	90-day dietary: **TGAI** tembotrione	NOEL = 64 ♂/76 ♀ mg/kg bw/d LOEL = 631 ♂/782 ♀ mg/kg bw/d	NOEL: 64 mg ai/kg bw (No conversion)	16.33 mg ai/kg bw	0.255	Not Exceeded
Rabbit	Developmental: (Reproduction): **TGAI** tembotrione	NOEL: 1 mg ai/kg bw (decreased faecal output and food consumption) LOEL: 10 mg ai/kg bw	LOEL: 10 mg ai/kg bw (No conversion)	3.806 mg ai/kg bw	0.3806	Not Exceeded
Vascular plants						
Vascular Plant	Seedling emergence: **EP** AE 0172747 02 SC 52 Herbicide	most sensitive monocot - EC_{25} (onion): > 0.031 kg ai/ha most sensitive dicot - EC_{25} (lettuce): 0.00044 kg ai/ha	EC_{25} (onion): 31 g ai/ha EC_{25} (lettuce): 0.44 g ai/ha	168.202 g ai/ha 168.202 g ai/ha	5.426 382.27	Exceeded Exceeded
	Vegetative vigour: **EP** AE 0172747 02 SC 52 Herbicide	most sensitive monocot - EC_{25} (onion): > 0.0056 kg ai/ha most sensitive dicot - EC_{25} (tomato): 0.00044 kg ai/ha	EC_{25} (onion): 5.6 g ai/ha EC_{25} (lettuce): 0.44 g ai/ha	168.202 g ai/ha 168.202 g ai/ha	30.036 382.27	Exceeded Exceeded

Table 16 Screening Level Risk Assessment for Aquatic Non-target Species

Organism	Exposure: Test Substance	Toxicity Endpoint Value	Converted Tox End point value	EEC	RQ Value	Level of Concern
Freshwater Invertebrates						
Daphnia magna	48-hour acute: **TGAI** tembotrione	EC_{50}: 48.9 mg ai/L	$EC_{50} \div 2 =$ 24.45 mg ai/L	0.02191 mg ai/L	0.000896	Not Exceeded
	48-hour acute: Transformation product **M6** (AE 0456148)	EC_{50}: > 115 mg ai/L	$EC_{50} \div 2 =$ 57.5 mg ai/L	0.02191 mg ai/L	0.000381	Not Exceeded
	48-hour acute: **EP** AE 0172747 02 SC 52 Herbicide	EC_{50}: 11.6 mg ai/L	$EC_{50} \div 2 =$ 5.8 mg ai/L	0.02191 mg ai/L	0.003778	Not Exceeded
	21-day chronic: **TGAI** tembotrione	NOEC: 5.10 mg ai/L (reduction in length of surviving parents)	NOEC: 5.10 mg ai/L (No conversion)	0.02191 mg ai/L	0.004296	Not Exceeded
	21-day chronic: Transformation product **M6** (AE 0456148)	NOEC: 113 mg ai/L (Immobilization) (Note: 113 mg ai/L is the highest test concentration)	NOEC: 113 mg ai/L (No conversion)	0.02191 mg ai/L	0.000194	Not Exceeded
Chironomids	28-day chronic: **TGAI** tembotrione	NOEC: 2.0 mg ai/L (emergence)	NOEC: 2.0 mg ai/L (No conversion)	0.02191 mg ai/L	0.01096	Not Exceeded
Freshwater Fish						
Rainbow trout	96-hour acute: **TGAI** tembotrione	LC_{50}: > 101mg ai/L (only concentration tested - limit test)	$LC_{50} \div 10 =$ 10.1 mg ai/L	0.02191 mg ai/L	0.002169	Not Exceeded
	96-hour acute: Transformation product **M6** (AE 0456148)	LC_{50}: > 105mg ai/L (only concentration tested - limit test)	$LC_{50} \div 10 =$ 10.1 mg ai/L	0.02191 mg ai/L	0.002087	Not Exceeded
	96-hour acute: **EP** AE 0172747 02 SC 52 Herbicide	LC_{50}: 1.83 mg ai/L	$LC_{50} \div 10 =$ 10.1 mg ai/L	0.02191 mg ai/L	0.1197	Not Exceeded

Organism	Exposure: Test Substance	Toxicity Endpoint Value	Converted Tox End point value	EEC	RQ Value	Level of Concern
Bluegill sunfish	96-hour acute: **TGAI** tembotrione	LC$_{50}$: > 100 mg ai/L (100mg ai/L was the only treatment)	LC$_{50}$ ÷ 10 = 10. mg ai/L	0.02191 mg ai/L	0.002191	Not Exceeded
Fathead minnow	Chronic - 34-day (ELS): **TGAI** tembotrione	NOEC: 0.604 mg ai/L (Fry survival - day 34)	NOEC: 0.604 mg ai/L (No conversion)	0.02191 mg ai/L	0.03627	Not Exceeded
Amphibians						
Fathead minnow (surrogate data)	Chronic - 34-day (ELS): **TGAI** tembotrione	NOEC: 0.604 mg ai/L (Fry survival - day 34)	NOEC: 0.604 mg ai/L (No conversion)	0.1168 mg ai/L	0.1934	Not Exceeded
Freshwater Algae						
Green alga	96-hour acute: **TGAI** tembotrione	EC$_{50}$: 0.31 mg a.i./L (cell density)	EC$_{50}$ ÷ 2 = 0.155 mg ai/L	0.02191 mg ai/L	0.1414	Not Exceeded
Green alga	72-hour acute: Transformation product **M6** (AE 0456148)	EC$_{50}$: > 103 mg ai/L (only concentration tested)	EC$_{50}$ ÷ 2 = 51.5 mg ai/L	0.02191 mg ai/L	0.000213	Not Exceeded
Green alga	72-hour acute: **EP** AE 0172747 02 SC 52 Herbicide	EC$_{50}$: 2.7 mg a.i./L (Cell density)	EC$_{50}$ ÷ 2 = 1.35 mg ai/L	0.02191 mg ai/L	0.01623	Not Exceeded
Diatom	120-hour: **TGAI** tembotrione	EC$_{50}$: 9 mg a.i./L (Biomass)	EC$_{50}$ ÷ 2 = 4.5 mg ai/L	0.02191 mg ai/L	0.004869	Not Exceeded
Aquatic Vascular Plants						
Lemna gibba G3	7-day: **TGAI** tembotrione	EC$_{50}$: 5.2 μg ai/L (frond number)	EC$_{50}$ ÷ 2 = 2.6 μg ai/L (0.0026 mg ai/L)	0.02191 mg ai/L	8.427	Exceeded
Lemna gibba G3	7-day: Transformation product **M6** (AE 0456148)	EC$_{50}$: > 105 mg ai/L (all endpoints) (only concentration tested - limit test)	EC$_{50}$ ÷ 2 = 52.5 mg ai/L	0.02191 mg ai/L	0.00042	Not Exceeded
Marine Organisms						
Crustacean (Mysid shrimp)	96-hour acute: **TGAI** tembotrione	LC$_{50}$: > 79 μg ai/L	LC$_{50}$ ÷ 2 = 39.5 μg ai/L (0.0395 mg ai/L)	0.02191 mg ai/L	0.5547	Not Exceeded
	Chronic - 28-day: **TGAI** tembotrione	NOEC: 5.7 μg ai/L (most sensitive endpoint - overall survival)	NOEC: 5.7 μg ai/L (0.0057 mg ai/L)	0.02191 mg ai/L	3.844	Exceeded

Organism	Exposure: Test Substance	Toxicity Endpoint Value	Converted Tox End point value	EEC	RQ Value	Level of Concern
Mollusc (Eastern oyster)	96-hour acute: **TGAI** tembotrione	EC_{50}: 39 mg ai/L (shell growth)	$EC_{50} \div 2 =$ 19.5 mg ai/L	0.02191 mg ai/L	0.001124	Not Exceeded
Marine Fish (Sheepshead minnow)	96-hour acute: **TGAI** tembotrione	LC_{50}: > 100 mg ai/L (limit test)	$LC_{50} \div 10 =$ 10 mg ai/L	0.02191 mg ai/L	0.002191	Not Exceeded
Marine diatom	96-hour acute: **TGAI** tembotrione	EC_{50}: 8.5 mg a.i./L (Cell density)	$EC_{50} \div 2 =$ 4.25 mg ai/L	0.02191 mg ai/L	0.005155	Not Exceeded

Table 17 Refined Risk Assessment on Non-Target Species exposed to drift of tembotrione

Organism (exposure)	Test Substance	Endpoint Value	EEC (6% drift)	RQ (Risk)	Level of Concern
Terrestrial Vascular Plants					
Onion *Allium cepa* (Seedling emergence)	**EP** AE 0172747 02 SC 52 Herbicide	EC_{25}: 31 g ai/ha	10.09 g ai/ha	0.3256 (Low)	Not Exceeded
Lettuce *Lactuca sativa* (Seedling emergence)	**EP** AE 0172747 02 SC 52 Herbicide	EC_{25}: 0.44 g ai/ha	10.09 g ai/ha	22.93 (High)	Exceeded
Onion *Allium cepa* (Vegetative vigour)	**EP** AE 0172747 02 SC 52 Herbicide	EC_{25}: 5.6 g ai/ha	10.09 g ai/ha	1.8018 (Moderate)	Exceeded
Tomato *Lycopersicon esculentum* (Vegetative vigour)	**EP** AE 0172747 02 SC 52 Herbicide	EC_{25}: 0.44 g ai/ha	10.09 g ai/ha	22.93 (High)	Exceeded
Freshwater and Marine Species					
Freshwater - Aquatic Vascular Plant *Lemna gibba* G3 (7-day Acute)	**TGAI** Tembotrione	EC_{50}: 5.2 µg ai/L ½ EC_{50} = 2.6 µg ai/L = 0.0026 mgai/L	0.0013146 mg ai/L	0.506 (Low)	Not Exceeded
Crustacean - Saltwater mysid *Americamysis bahia* (28-day Chronic)	**TGAI** Tembotrione	NOEC: 5.7 µg ai/L = 0.0057 mg ai/L	0.0013146 mg ai/L	0.2306 (Low)	Not Exceeded

Table 18 Refined Risk Assessment on Non-Target Species exposed to runoff of tembotrione

Organism (exposure)	Test Substance	Endpoint Value	EEC 90th percentile concentrations (µg ai/L)	RQ (Risk)	Level of Concern
Freshwater and Marine Species					
Freshwater -Aquatic Vascular Plant *Lemna gibba* G3 (7-day Acute)	**TGAI** Tembotrione	EC50: 5.2 µg ai/L (½ EC50 = 2.6 µg ai/L)	6.3 µg/L	2.42 (Moderate)	Exceeded
Crustacean - Saltwater mysid *Americamysis bahia* (28-day Chronic)	**TGAI** Tembotrione	NOEC: 5.7 µg ai/L (no conversion)	6.1 µg/L	1.07 (Moderate)	Exceeded

Table 19 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
			Tembotrione
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes[1]
Predominantly anthropogenic[2]	Yes		Yes[2]
Persistence[3]:	Soil	Half-life ≥ 182 days	80th percentile of six laboratory soil values: 127 days
	Water	Half-life ≥ 182 days	12-64 days
	Sediment	Half-life ≥ 365 days	41-139 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (1.1×10^{-8} Pa at 20°C) and Henry's Law Constant (1.69×10^{-6} Pa × m^3/mol at 20°C).

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Active Ingredient Endpoints**
		Tembotrione
Bioaccumulation[4]	Log $K_{OW} \geq 5$	-1.07 at pH 7
	BCF $\geq$ 5000	Value not available
	BAF $\geq$ 5000	Value not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?		No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

Table 20 Alternative Herbicides for Grass and Broadleaf Weed Control in Corn

Technical Grade Active Ingredient	**End-use Product(s)**	**Weed Claims**	**Herbicide Classification**	
			Group	**Mode of Action**
Nicosulfuron	Accent	Annual grasses plus quackgrass	2	ALS inhibitor
Rimsulfuron	Elim	Annual grasses plus lamb's-quarters and redroot pigweed	2	ALS inhibitor
Nicosulfuron + rimsulfuron	Ultim	Annual grasses plus quackgrass and redroot pigweed	2	ALS inhibitor
Prosulfuron	Peak	Broadleaf weeds	2	ALS inhibitor
s-metolachlor	Dual II Magnum	American nightshade, fall panicum, eastern black nightshade, foxtail, crabgrass, old witchgrass, barnyard grass, yellow nutsedge and redroot pigweed	15	Inhibition of cell division (VLCFA inhibition)
Dimethenamid	Frontier	Foxtail (green, yellow, giant), fall panicum, crabgrass (smooth, large), redroot pigweed, old witchgrass, eastern black nightshade, barnyard grass and yellow nutsedge	15	Inhibition of cell division (VLCFA inhibition)
Flufenacet	Flufenacet	green foxtail, redroot pigweed, and lamb's-quarters	15	Inhibition of cell division (VLCFA inhibition)
Atrazine	Aatrex	Broadleaf weeds and wild oats	5	Inhibitors of photosynthesis at photosystem II Site A
Dicamba	Banvel	Broadleaf weeds	4	Synthetic auxin
Dicamba Diflufenzopyr	Distinct	Broadleaf weeds	4 4	Synthetic auxin

Technical Grade Active Ingredient	End-use Product(s)	Weed Claims	Herbicide Classification	
			Group	Mode of Action
Atrazine Dicamba	Marksman	Broadleaf weeds	5 4	Synthetic auxin
Topramezone	Impact	Broadleaf weeds and grasses	27	HPPD inhibition
Mesotrione	Callisto	Broadleaf weeds	27	HPPD inhibition
Isoxaflutole	Converge	Broadleaf weeds	27	HPPD inhibition

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Five of the specified Canadian MRLs are the same as those in the U.S. In six cases, the MRL differs from the tolerance established in the US (40 CFR Part 180).

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex[a] (ppm)
Sweet corn kernels plus cob with husks removed	0.04	0.01	Not reviewed by Codex
Meat and fat of cattle, goats, hogs, horses, sheep and poultry	0.02	NR (not required)	
Meat byproducts of hogs	0.02	NR	
Meat byproducts (except liver) of poultry	0.02	NR	
Eggs	0.02	NR	
Milk	0.02	NR	

[a] Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1270322	2006, BCS-DER Product Chemistry-AE 0172747 (tembotrione) technical herbicide, 201531, DACO: 2.0 CBI
1270323	2006, BCS-DER Product Chemistry-AE 0172747 (tembotrione) technical herbicide, 201531, DACO: 2.0 CBI
1270324	2006, BCS-DER Product Chemistry-AE 0172747 (tembotrione) technical herbicide, 201531, DACO: 2.0 CBI
1270463	2005, Product chemistry of AE 0172747 technical, BR 2437, MRID: 46695401, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.13.1,2.13.2,2.13.3,2.13.4,2.4,2.5,2.6,2.7,2.8,2.9 CBI
1270472	2005, Product chemistry of AE 0172747 technical, BR2423, MRID: 46695402, DACO: 2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6, 2.14.7,2.14.8,2.14.9 CBI
1335722	2006, Supplemental Product Chemistry of AE 0172747 Technical, BR 2545, DACO: 2.11,2.11.2,2.13.2,2.13.4 CBI
1433035	2006, CAS Inventory Service Report for Tembotrione and Metabolite, N, DACO: 2.5,2.6 CBI
1442961	2006, CAS Inventory Service Report for Tembotrione and Metabolite, N, DACO: 2.5,2.6 CBI
1270453	2005, In house laboratory validation of an analytical method for the determination of residues of AE 0172747 and its metabolites AE 0456148, AE 0968400, AE 1124336, AE 0941989 and AE 1392936 in soil using LC/MS/MS and GC/MSD, 03RAAEX022, MRID: 46965521, D
1270454	2005, Independent laboratory validation of method AE-005-W05-02 for the determination of AE 0172747 and its metabolites AE 0456148 and AE 1392936 in water, MR-091/05, MRID: 46695526, DACO: 8.2.2.3,8.6
1270455	2005, Independent laboratory validation of method AE002-S04-02 for the determination of AE 0172747 and its metabolites AE 0456148, AE 0968400, AE 1392936, AE 0941989 by HPLC-MS/MS and for determination of AE 1124336 by GC/MSD in soil, MR-181/04, MRID: 466

1270456	2005, Method of analysis for the determination of residues of AE 0172747 and its metabolites AE 0456148 and AE 1392936 in water using LC/MS/MS - revision W05-03, AE-005-W05-03, MRID: 46695524, DACO: 8.2.2.3,8.6
1270457	2005, AE 0172747: Analytical method for the determination of AE 0172747 and its metabolites AE 0456148, AE 0968400, AE 1392936, AE 0941989 by LC/MS/MS and for the determination of AE 1124336 by GC/MSD in soil, AE002-S04-03, MRID: 46695523, DACO: 8.2.2.1,8
1270458	2005, In house laboratory validation of an analytical method for the determination of residues of AE 0172747 and its metabolites AE 0456148 and AE 1392936 in water using LC/MS/MS, RAAEX021, MRID: 46695522, DACO: 8.2.2.3,8.6
1292897	2006, AE 0172747 Herbicide - Analytical Methodology (parent compound and transformation products) -Sediment: Data Waiver Request, DACO: 8.2.2.2 CBI
1408734	2007, Confidential buisness information section for - Product chemistry of SC 547 herbicide, DACO: 3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,3.5.4,Document H,Document J,IIIA 1.4.1,IIIA 1.4.2,IIIA 1.4.4,IIIA 1.4.5.1,IIIA 1.4.5.2,IIIA 1.5 CBI
1408736	2007, Product chemistry of SC 547 herbicide, DACO: 3.3.1,3.3.2,3.4.1,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9,Document J,IIIA 1.4.2,IIIA 2.1,IIIA 2.11,IIIA 2.12,IIIA 2.13,IIIA 2.14,IIIA 2.2.1,IIIA 2.2.2,III
1608014	2007, Product chemistry, DACO: 3.0,3.2,3.3.1,3.4 CBI
1608022	2006, Physical Properties of Thiencarbazone-methyl + [CBI removed] 00 10 + 60 gn (BYH 18636 00), DACO: 3.5.1,3.5.11,3.5.12,3.5.13,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9 CBI
1608023	2006, GLP protocol - Physical & Chemical Properties for [CBI removed] + BYH 18636 WG42 + 21, DACO: 3.5.1,3.5.11,3.5.12,3.5.13,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9 CBI
1608024	2006, GLP protocol - Physical & Chemical properties of BYH18636+AE 0172747+[CBI removed] SC, DACO: 3.5.1,3.5.11,3.5.12,3.5.13,3.5.15,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9 CBI
1608025	2002, Standard Test Methods for Flash Point by Pensky-Martens Closed Cup Tester, DACO: 3.5.11,3.5.12
1608026	2007, Determination of pH of Water, Flowables, and Aqueous Solutions, DACO: 3.5.7 CBI
1608027	2004, Brookfield Viscosity, DACO: 3.5.9 CBI
1608028	2001, OHAUS LOOSE BULK DENSITY - TM: A-5.09-03, DACO: 3.5.6 CBI
1608029	2004, Specific Gravity of Liquids, DACO: 3.5.6 CBI
1608030	2000, BULK ODOR, DACO: 3.5.3 CBI
1608031	1998, BAYER ANALYTICAL METHOD: CROSS-REFERENCE - TM A-39-01 APPEARANCE, DACO: 3.5.2 CBI

1672976	2008, Storage Stability and Corrosion Characteristics of Thiencarbazone-Methyl +Tembotrione + [CBI removed] SC, DACO: 3.5.10,3.5.14 CBI

2.0 Human and Animal Health

1270384	2005, Tier 2 Summary of the Acute Toxicological Studies on the Active Substance and metabolites for AE 0172747, M-260932-01-1, DACO: 4.1
1270385	2005, Tier 2 Summary of the Acute Toxicological Studies on the Active Substance and metabolites for AE 0172747, M-260932-01-1, DACO: 4.1
1270386	2005, BCS DERs for AE 0172747-TOXICOLOGY-ALL in pdf, JAB05002, MRID: 46995743, DACO: 4.1
1270387	2005, Evaluation of acute and chronic dietary exposure to AE 0172747 and assessment of potential risk, RAAEX028, MRID: 46695746, DACO: 4.2.1,4.4.1,4.8
1270441	2005, Overview of Mammalian Toxicology for AE 0172747, 201409, MRID: 46695742, DACO: 4.8
1270442	2005, Scientific advisory group review of the thyroid and kidney from chronic/carcinogenicity studies with AE 0172747 in the rat and dog, 393-043, MRID: 46695741, DACO: 4.8
1270443	2005, Statement on chronic progressive nephropathy in the rat, M-260119-01-2, MRID: 46695740, DACO: 4.8
1270449	2005, AE 0172747: In vitro inhibition of HPPDase using liverbeads from different species, SA 05068, MRID: 46695734, DACO: 4.8
1270450	2005, AE 1417268, AE 0456148 and AE 1392936 - Assessment of HPPDase - Inhibition in the rat (part A, B & C), SA 04132, MRID: 46695733, DACO: 4.8
1270451	2005, AE 0172747 - Effect on blood tyrosine level in pregnant rabbit after oral administration by gavage, SA 03315, MRID: 46695732, DACO: 4.8
1270452	2005, AE 0172747 - Effects on blood coagulation parameters with and without administration of vitamin K1, SA04296, MRID: 46695731, DACO: 4.8
1270611	2005, AE1417268 - Acute toxicity in the rat after oral administration, AT01702, MRID: 46695621, DACO: 4.2.1,4.6.1
1270614	2005, AE 0456148 - Acute toxicity in the rat after oral administration, AT01510, MRID: 46695620, DACO: 4.2.1,4.6.1
1270615	2003, An acute oral LD50 study in the rat with AE 0172747, 200400, MRID: 46695618, DACO: 4.2.1,4.6.1
1270616	2005, AE 0456148 - Acute toxicity in the rat after dermal application, AT02537, MRID: 46695625, DACO: 4.2.2,4.6.2
1270618	2003, An acute dermal LD50 study in the rat with AE 0172747, 200403, MRID: 46695623, DACO: 4.2.2,4.6.2

1270619	2005, AE 0172747 00 1C95 0002 - Acute inhalation toxicity (nose only) study in the rat, 1702/005, MRID: 46695626, DACO: 4.2.3,4.6.3
1270620	2005, AE 0456148 - Acute eye irritation on rabbits, AT01860, MRID: 46695630, DACO: 4.2.4,4.6.4
1270621	2005, AE 0172747 - Eye irritation to the rabbit, AES 115/023773, MRID: 46695628, DACO: 4.2.4,4.6.4
1270622	2005, AE 0456148 - Acute skin irritation/corrosion on rabbits, AT01805, MRID: 46695633, DACO: 4.2.5,4.6.5
1270623	2005, AE 0172747 - Skin irritation to the rabbit, AES 114/023583, MRID: 46695631, DACO: 4.2.5,4.6.5
1270624	2005, AE 0456148 (Project. AE 0172747) - Local lymph node assay in mice (LLNA/IMDS), AT01750, MRID: 46695636, DACO: 4.2.6,4.6.6
1270625	2005, AE 0172747 - Guinea-pig skin sensitization study (Magnusson & Kligman method), AES 116/023862, MRID: 46695634, DACO: 4.2.6,4.6.6
1270626	2005, AE 1417268 (metabolite of AE 0172747) - 28-day toxicity study in the rat by dietary administration, SA04266, MRID: 46695637, DACO: 4.3.3
1270627	2005, AE 1417268 (Metabolite of AE 0172747) 90-day toxicity study in the rat by dietary administration, SA05004, MRID: 46995641, DACO: 4.3.1,4.7.1
1270638	2005, AE 0172747 - 90-day toxicity study in the rat by dietary administration, SA 01170, MRID: 46995638, DACO: 4.3.1,4.7.1
1270649	2005, AE 0172747 - 90-day toxicity study in the mouse by dietary administration, SA01431, MRID: 46695640, DACO: 4.3.1,4.7.1
1270659	2005, AE 0172747 - 90-day toxicity study in the rat by dietary administration, SA05002, MRID: 46695639, DACO: 4.3.1,4.7.1
1270660	2005, AE 0172747 - 90-day toxicity study in the dog by dietary administration, SA 02162, MRID: 46695443, DACO: 4.3.2,4.7.2
1270661	2005, AE 0172747 - subacute toxicity study in the rat (4 weeks dermal administration), AT02587, MRID: 46695645, DACO: 4.3.5,4.7.4
1270662	2005, AE 0172747 - Project: AE 0172747 - Subacute toxicity study in the rat (4 weeks dermal administration), AT02011, MRID: 46695644, DACO: 4.3.5,4.7.4
1270676	2005, AE 0172747 - Developmental toxicity study in the rabbit by gavage, SA 02056, MRID: 46695703, DACO: 4.5.2,4.5.3
1270677	2005, AE 0172747 - Complementary range-finding study for developmental toxicity in the rabbit by gavage, SA 02041, MRID: 46695702, DACO: 4.5.2,4.5.3
1270678	2005, AE 0172747 - Range-finding study for developmental toxicity in the rabbit by gavage, SA 01279, MRID: 46695701, DACO: 4.5.2,4.5.3
1270691	2005, AE 0172747 - Developmental toxicity study in the rat by gavage, SA 02226, MRID: 46695647, DACO: 4.5.2,4.5.3

1270692 2005, AE 0172747 - Range-finding study for developmental toxicity in the rat by gavage, SA 01280, MRID: 46695646, DACO: 4.5.2,4.5.3

1270693 2005, Technical grade AE0172747: A two-generation reproductive toxicity study in the wistar rat, 201266, MRID: 46695704, DACO: 4.5.1,4.8

1270712 2005, AE 0172747 - Chronic toxicity study in the dog by dietary administration, SA03352, MRID: 46695705, DACO: 4.3.2,4.4.1,4.7.2

1270726 2005, Carcinogenicity study of AE 0172747 in the C57BL/6 mouse by dietary administration, SA02256, MRID: 46695706, DACO: 4.4.2,4.4.3

1270730 2005, Chronic toxicity and carcinogenicity study of AE 0172747 in the male wistar rat by dietary administration, SA02400, MRID: 46695708, DACO: 4.4.4

1270733 2005, Chronic toxicity and carcinogenicity study of AE 0172747 in the Wistar rat by dietary administration, SA02055, MRID: 46695707, DACO: 4.4.4

1270734 2005, AE 1392936 (Project: AE 0172747) - Salmonella/Microsome test - Plate incorporation and preincubation method, AT02552, MRID: 46695712, DACO: 4.5.4

1270735 2005, AE 1417268 (project: AE 0172747) - Salmonella/microsome test (plate incorporation and preincubation method), AT01713, MRID: 46695711, DACO: 4.5.4

1270736 2005, AE 0456148 (Project: AE 0172747) - Salmonella/microsome test - Plate incorporation and preincubation method, AT01610, MRID: 46695710, DACO: 4.5.4

1270737 2005, Technical AE 0172747 - Bacterial reverse mutation test, AES117/023631, MRID: 46695709, DACO: 4.5.4

1270738 2005, AE 1392936 (Project: AE 0172747) - V79/HPRT-test in vitro for the detection of induced forward mutations, AT02433, MRID: 46695716, DACO: 4.5.5

1270739 2005, AE 1417268 - Mutation at the Thymidine Kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the Microtitre fluctuation technique, 2014/89, MRID: 46695715, DACO: 4.5.5

1270740 2004, AE 0456148 (Project: AE 0172747) - V79/HPRT-test in vitro for the detection of induced forward mutations - TXAEP007, AT01738, MRID: 46695714, DACO: 4.5.5

1270741 2005, Technical AE 0172747 - Mammalian cell mutation assay, AES119/024223, MRID: 46695713, DACO: 4.5.5

1270742 2005, AE 1392936 00 1C94 0001 (Project: AE 0172747) - In vitro chromosome aberration test with chinese hamster V79 cells, AT02214, MRID: 46695720, DACO: 4.5.6

1270743 2005, AE 1417268: Induction of chromosome aberrations in cultured human peripheral blood lymphocytes, 2014/88, MRID: 46695719, DACO: 4.5.6

1270744	2005, AE 0456148 (Project: AE 0172747) - In vitro chromosome aberration test with Chinese hamster V79 cells - TXAEP012, AT01906, MRID: 46695718, DACO: 4.5.6
1270745	2005, Technical AE 0172747 - In vitro mammalian chromosome aberration test in human lymphocytes, AES118/024021, MRID: 46695717, DACO: 4.5.6
1270746	2005, Technical AE 0172747 - Mouse micronucleus test, AES120/023519, MRID: 46695721, DACO: 4.5.7
1270747	2005, AE 0172747 (Project: AE 0172747) - Unscheduled DNA synthesis test with rat liver cells in vivo, AT02169, MRID: 46695722, DACO: 4.5.8
1270748	2005, A subchronic neurotoxicity screening study with technical grade AE0172747 in Wistar rats, 201174, MRID: 46695724, DACO: 4.5.12,4.5.13
1270749	2005, An acute oral neurotoxicity screening study with technical grade AE 0172747 in Wistar rats, 201248, MRID: 46695723, DACO: 4.5.12,4.5.13
1270750	2005, A developmental neurotoxicity screening study with technical grade AE0172747 in wistar rats, 201310, MRID: 46695725, DACO: 4.5.14
1270751	2005, AE 0172747 - Single oral low and high dose - Rat A.D.M.E. study, SA 02092, MRID: 46695729, DACO: 4.5.9
1270752	2005, AE 0172747 - Rat blood / plasma kinetics study, SA 02096, MRID: 46695728, DACO: 4.5.9
1270753	2005, [Cyclohexyl-UL-14C]AE 0172747: Absorption, distribution, excretion and metabolism in the rat, MEF-04/512, MRID: 46695727, DACO: 4.5.9
1270754	2005, [Cyclohexyl-UL-14C]AE 0172747: Rat blood/plasma kinetics study, MEF-04/437, MRID: 46695726, DACO: 4.5.9
1270389	BCS-DERs for AE 0172747 -RESIDUE+METABOLISM-ALL in pdf
1270437	AE 0172747: Overview of the metabolism and magnitude of residues in plants and animals
1270414	BCS DER-RES-cow-Study RAAEX040
1270415	BCS DER-RES-cow-Study RAAEX040
1270416	BCS DER-RES-hen-Study RAAEX041
1270417	BCS DER-RES-hen-Study RAAEX041
1270418	BCS DER-RES-M5 cow-Study BAG-395-052591
1270419	BCS DER-RES-M5 cow-Study BAG-395-052591
1270568	Metabolism of [phenyl-UL-14C]-AE 0172747 in corn (Zea mays) after treatment with an application rate of 100 g a.i./ha and 200 g a.i./ha in presence of safener isoxadifen-ethyl (AE F122006)
1270569	[Phenyl-U-14C]-AE 0172747: Absorption, distribution, metabolism and excretion following repeated oral administration to the laying hen

1270572	Metabolism of [cyclohexyl-UL-14C]-AE 0172747 in corn (Zea mays) after treatment with an application rate of 200 g a.i./ha in presence of safener isoxadifen-ethyl (AE F122006)
1270573	(14C)-AE 1417268:- Absorption, distribution, metabolism and excretion following repeated oral administration to the lactating cow
1270574	[Cyclohexyl-U-14C]-AE 0172747: Absorption, distribution, metabolism and excretion following repeated oral administration to the laying hen
1270575	[Phenyl-U-14C]-AE 0172747: Absorption, distribution, metabolism and excretion following repeated oral administration to the lactating cow
1270576	[Cyclohexyl-U-14C]-AE 0172747: Absorption, distribution, metabolism and excretion following repeated oral administration to the lactating cow
1270594	AE0172747 - Magnitude of the residue in lactating cows
1270596	M-5 - Residues in milk and tissues of dairy cows
1270599	AE 0172747 - magnitude of the residue in laying hens
1312171	Development and Validation of a Residue Enforcement Method for the Determination of Residues of AE 0172474 and its Metabolites in/on Animal Material by HPLC-MS/MS. Demonstration of a LC/MS/MS Confirmatory Method.
1270402	BCS DER-AnalytMeth-Beef & Milk Method
1270403	BCS DER-AnalytMeth-Beef & Milk Method
1270404	BCS DER-AnalytMeth-plant
1270405	BCS DER-AnalytMeth-plant
1270406	BCS DER-AnalytMeth-poultry
1270407	BCS DER-AnalytMeth-poultry
1270408	BCS DER-AnalytMeth-ILVanimal-Study RAAEX055
1270409	BCS DER-AnalytMeth-ILVanimal-Study RAAEX055
1270577	ILV of the Bayer CropScience method no. 0096 for the determination of residues of AE 0172747 and its metabolite AE 1417268 in/on animal material by HPLC-MS/MS. Demonstration of a LC/MS/MS confirmatory method.
1270578	AE 0172747: Validation of analytical method AE/03/01 for AE 0172747 and its major metabolites AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in plant matrices using LC/MS/MS
1270581	Independent method validation of Bayer method numbers AE-003-A04-01 - AE 0172747: An analytical method for the determination of residues of AE 0172747 in beef tissues and milk matrices using LC/MS/MS
1270582	Independent laboratory validation of method 201059, AE 0172747: An analytical method for the determination of residues of AE 0172747 and its major

	metabolites AE 0456148, AE 1417268, and AE 1392936 in plant matrices using LC/MS/MS for AE 01
1270583	Independent laboratory validation of AE 0172747: An analytical method for the determination of residues of AE 0172747 in poultry tissues and egg matrices
1270584	Extraction efficiency of Bayer method AE/03/01 AE 0172747: Analytical method for the determination of residues of AE 0172747 and its metabolites AE 0456148, AE 1417268 and AE 1392936 in plants matrices using LC/MS/MS
1270585	Bayer method AE-004-A04-01 - AE 0172747 : An analytical method for the determination of residues AE 0172747 in poultry tissues and egg matrices using LC/MS/MS
1270586	AE 0172747 : An analytical method for the determination of residues of AE 0172747 in beef tissues and milk matrices using LC/MS/MS
1270587	AE 0172747: An analytical method for the determination of residues of AE 0172747 and its major metabolites AE 0456148, AE 1417268, and AE 1392936 in plant matrices using LC/MS/MS
1270588	[Cyclohexyl-UL14C]AE 0172747: Extraction efficiency of the residue analytical method for the determination of AE 0172747 in animal tissues and egg matrices using aged residues
1270589	Evaluation of AE 0172747 and relevant metabolites FDA multiresidue method (MRM) testing
1270410	BCS DER-Storage Stability-Corn-Study RAAEX034
1270411	BCS DER-Storage Stability-Corn-Study RAAEX034
1270412	BCS DER-Storage Stability-Vegetables-Study RAAEX035
1270413	BCS DER-Storage Stability-Vegetables-Study RAAEX035
1270591	Stability of AE 0172747, AE 0456148, AE 0968400, AE 1124336, AE 0941989 and AE 1392936 in soil during frozen storage, USA, 2003 (Reported through a maximum of 660 days storage)
1270592	Storage stability of AE 0172747, AE 0456148 (M6), AE 1417268 (M5), and AE 1392936 (M2) in turnip roots, mustard greens and yellow squash
1270593	Storage stability of AE 0172747, AE 0456148 (M6), AE 1417268 (M5) and AE 1392936 (M2) in corn grain, forage and fodder
1427599	Isoxadifen-ethyl ¿¿¿ Magnitude of the Residue in Sweet Corn and Popcorn (Amended Report)
1270421	BCS DER-RES-field corn-Study RAAEX010
1270422	BCS DER-RES-sweet corn- Study RAAEX026
1270423	BCS DER-RES-sweet corn- Study RAAEX026
1270424	BCS DER-RES-pop corn-Study RAAEX015
1270425	BCS DER-RES-pop corn-Study RAAEX015

1270434	BCS DER-RES-rotational crops-field-Study RAAEY002
1270420	BCS DER-RES-field corn-Study RAAEX010
1270600	AE 0172747: Magnitude of residues in popcorn resulting from foliar applications of AE 0172747 02 SC52 A1 under maximum proposed label specifications (2003)
1270601	AE 0172747: Magnitude of residues in sweet corn resulting from foliar application of AE 0172747 02 SC52 A1 under maximum proposed label specifications (2003)
1270602	AE 0172747 - Magnitude of residues in field corn resulting from foliar applications of AE 0172747 02 SC52 A1 under maximum proposed label specifications (2003)
1270431	BCS DER-RES-confined rot crop-Study MEAEX007
1270432	BCS DER-RES-confined rot crop-Study MEAEX007
1270433	BCS DER-RES-rotational crops-field-Study RAAEY002
1270435	BCS DER-RES-rotational crops-field-Study RAAEX012
1270436	BCS DER-RES-rotational crops-field-Study RAAEX012
1270609	AE 0172747: Magnitude of residues in mustard greens, turnips, summer squash, and bell peppers when used as rotational crops behind corn that was treated with AE 0172747 02 SC52 A1 at the maximum proposed label specifications (2003)
1270610	AE 0172747: Magnitude of residues in winter wheat when used as a rotational crop after corn that has had Foliar applications of AE 0172747 02 SC52 A1 at the maximum proposed label specifications (2003)
1270427	BCS DER-RES-processed corn-Study RAAEX011
1270428	BCS DER-RES-processed corn-Study RAAEX011
1270429	BCS DER-RES-processed wheat-Study RAAEY001
1270430	BCS DER-RES-processed wheat-Study RAAEY001
1270605	AE 0172747: Magnitude of residues in processed wheat fractions when used as a rotational crop after field corn that has had exaggerated rate applications of AE 0172747 02 SC52 A1 (2003)
1270606	AE 0172747: Magnitude of residues in processed corn fractions following exaggerated rate applications of AE 0172747 02 SC52 A1 (2003) (including residue reduction information)
1270438	AE 0172747: Determination of half-life in corn
1270608	The accumulation of [U-14C-phenyl]-AE 0172747 in confined rotational crops
1270439	Human health risk assessment for use on field corn, sweet corn and popcorn
1270755	2005, AE 0172747 & [safener]SC 420 + 210 formulation - In vivo dermal absorption study in the male rat, DACO: 5.8
1274638	Canadian Use Description Scenario for AE 0172747 02 SC 52 Herbicide

1514346	EPA-Policy Science Advisory Council for Exposure
1514347	PMRA Operator Risk for AE0172747 corn herbicide

3.0 Environment

PMRA Document Number	Reference
1270325	2006, Tier 2 summary of fate and behaviour in the environment for the active substance AE 0172747, DACO: 8.1 CBI
1270327	2006, Tier 2 summary of fate and behaviour in the environment for the active substance AE 0172747, DACO: 8.1
1270328	2006, Tier 2 summary of fate and behaviour in the environment for the active substance AE 0172747, DACO: 8.1
1270459	2005, AE 0172747 - Fate and behavior in the environment, DACO: 8.6
1270492	2005, [14C]-AE 1392936: Adsorption to and desorption from four soils, DACO: 8.2.2.2,8.2.4.2
1270493	2005, [14C]-AE 1124336: Adsorption/desorption to and from five soils, DACO: 8.2.2.2,8.2.4.2
1270494	2005, [14C]-AE 0968400: Adsorption/desorption to and from five soils, DACO: 8.2.2.2,8.2.4.2
1270495	2005, [14C]-AE 0941989: Adsorption/desorption in four soils, DACO: 8.2.2.2,8.2.4.2
1270496	2005, [14C]-AE 0456148: Adsorption to and desorption from five soils, DACO: 8.2.2.2,8.2.4.2
1270497	2003, Adsorption/desorption of (phenyl-UL-14C)AE 0172747 in six soils and a sediment, DACO: 8.2.2.2,8.2.4.2
1270499	2005, Abiotic hydrolysis of 14C-AE 0172747 in buffered aqueous solutions at pH 4, pH 7, and pH 9, DACO: 8.2.3.2
1270500	2005, Phototransformation of AE 0172747 in sterile water buffered at pH 7, DACO: 8.2.3.3.2
1270501	2004, (Cyclohexyl-UL-14C) AE0172747: Phototransformation on soil, DACO: 8.2.3.3.1
1270502	2004, [Phenyl-UL-14C]AE 0172747: Phototransformation on soil, DACO: 8.2.3.3.1
1270504	2005, [14C]-AE 1392936: Rate of degradation in three soils at 20 degrees, DACO: 8.2.3.4.2

1270505	2005, [14C]-AE 0941989: Rate of degradation in three soils at 20 degrees, DACO: 8.2.3.4.2
1270506	2005, The route and rate of degradation of [Phenyl-U-14C]AE 0172747 in two US soils and [Cyclohexyl-U-14C]AE 0172747 in one soil under laboratory aerobic conditions at 25¿¿ C, DACO: 8.2.3.4.2
1270507	2005, Rate of degradation of [phenyl-U-14C]-AE 0172747 in three European soils under aerobic laboratory conditions at 20 degree C, DACO: 8.2.3.4.2
1270508	2005, Route and rate of degradation of [phenyl-U-14C]-AE 0172747 and [cyclohexyl-U-14C]-AE 0172747 in one European soil under aerobic laboratory conditions at 20 degree C and 10 degree C, DACO: 8.2.3.4.2
1270509	2004, [Phenyl-UL-14C]AE0172747: Anaerobic soil metabolism, DACO: 8.2.3.4.4
1270510	2005, [Cyclohexyl-UL-14C]AE0172747: Anaerobic soil metabolism, DACO: 8.2.3.4.4
1270511	2005, [cyclohexyl-U-14C]- and [phenyl-U-14C]-AE 0172747 Aerobic aquatic metabolism in sediment system Rhein, DACO: 8.2.3.5.2,8.2.3.5.4
1270512	2005, [cyclohexyl-U-14C]- and [phenyl-U-14C]-AE 0172747 - Aerobic aquatic metabolism in a fine sediment system, DACO: 8.2.3.5.2,8.2.3.5.4
1270513	2005, [Cyclohexyl-UL-14] AE 0172747: Anaerobic aquatic metabolism, DACO: 8.2.3.5.5,8.2.3.5.6
1270514	2005, [Phenyl-UL-14C]AE0172747: Anaerobic aquatic metabolism, DACO: 8.2.3.5.5,8.2.3.5.6
1270515	2005, Terrestrial field dissipation of AE 0172747 at four locations in the United States, DACO: 8.3.2.1,8.3.2.2,8.3.2.3
1292898	2006, AE 0172747 Herbicide - Laboratory Studies of Mobility -Soil Column Leaching : Data Waiver Request, DACO: 8.2.4.3
1581360	2005, Route and rate of degradation of [phenyl-U-14C]-AE 0172747 and [cyclohexyl-U-14C]-AE 0172747 in one European soil under aerobic laboratory conditions at 20 degree C and 10 degree C, DACO: 8.2.3.4.2 CBI
1581361	2005, Rate of degradation of [phenyl-U-14C]-AE 0172747 in three European soils under aerobic laboratory conditions at 20 degree C, DACO: 8.2.3.4.2 CBI
1270329	2006, Tier 2 summary of the ecotoxicological studies on the active substance for AE 0172747, DACO: 9.1
1270330	2006, Tier 2 summary of the ecotoxicological studies on the active substance for AE 0172747, DACO: 9.1
1270331	2006, Tier 2 summary of the ecotoxicological studies on the active substance for AE 0172747, DACO: 9.1
1270524	2004, Acute toxicity of AE 0456148 to the waterflea (Daphnia magna) under static conditions, DACO: 9.3.2,9.3.4,9.3.5,9.5.4,9.8.6

1270525 2005, Acute toxicity of AE 0172747 & isoxadifen-ethyl SC 420+210 to the waterflea Daphnia magna in a static laboratory test system, DACO: 9.3.2,9.3.4,9.3.5,9.5.4,9.8.6

1270526 2002, AE 0172747 - Acute toxicity to Daphnia magna (waterflea) under static testing conditions, DACO: 9.3.2,9.3.4,9.3.5,9.5.4,9.8.6

1270527 2003, AE 0172747 - Acute toxicity to eastern oysters (Crassostrea virginica) under flow-through conditions, DACO: 9.4.2,9.4.3,9.4.4,9.4.6,9.5.4

1270529 2005, AE 0172747 - Acute toxicity to mysids (Americamysis bahia) under flow-through conditions, DACO: 9.4.2,9.4.3,9.4.4,9.4.6,9.5.4

1270530 2005, AE 0172747 - Acute toxicity to sheepshead minnow (Cyprinodon variegatus) under static-renewal conditions, DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6

1270531 2005, Acute toxicity of AE 0456148 to fish (Oncorhynchus mykiss) under static conditions (product code: AE 0456148 00 1B99 0002), DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6

1270532 2005, Acute toxicity of AE 0172747 & Isoxadifen-ethyl SC 240+210 to fish (Oncorhynchus mykiss) under static conditions (product code: AE 0172747 02 SC52 A105), DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6

1270533 2003, Acute toxicity of AE 0172747 technical substance to fish (Oncorhynchus mykiss) (product code AE 0172747 00 1C97 0001), DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6

1270534 2003, Acute toxicity of AE 0172747 technical substance to fish (Lepomis macrochirus) (Product code AE 0172747 00 1C97 0001), DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6

1270536 2004, Chronic toxicity of AE 0456148, a metabolite of AE 0172747, to the Daphnia magna under static renewal conditions, DACO: 9.3.3

1270537 2003, Influence of AE 0172747 (tech.) on development and reproductive output of the waterflea Daphnia magna in a static renewal laboratory test system, DACO: 9.3.3

1270539 2004, AE 0172747 - Life-cycle toxicity test with mysids (Americamysis bahia), DACO: 9.4.5

1270540 2003, Early-life stage toxicity of AE 0172747 technical substance to fish (Pimephales promelas) (product code AE 0172747 00 1C94 0003), DACO: 9.5.3.1

1270542 2005, An acute oral toxicity study with the northern bobwhite: AE 0172747; substance, technical; product code: AE 0172747 00 1C97 0001, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,9.6.4

1270543 2005, An acute oral toxicity study with the mallard: AE 0172747; substance, technical; product code: AE 0172747 00 1C97 0001, DACO: 9.6.2.1,9.6.2.2,9.6.2.3,9.6.4

1270544	2005, A dietary LC50 study with the northern bobwhite: AE 0172747; substance technical; product code: AE 0172747 00 1C94 0002, DACO: 9.6.2.4,9.6.2.5
1270545	2005, A dietary LC50 study with the mallard: AE 0172747; substance, technical; product code: AE 0172747 00 1C94 0002, DACO: 9.6.2.4,9.6.2.5
1270546	2005, AE 0172747: A subchronic toxicity study with the mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3
1270547	2005, AE 0172747; Substance technical; Product code: AE 0172747 00 1C94 0002: A reproduction study with the mallard, DACO: 9.6.3.1,9.6.3.2,9.6.3.3
1270550	2005, AE 0172747; Substance technical; Product code: AE 0172747 00 1C94 0002: A reproduction study with the northern bobwhite, DACO: 9.6.3.1,9.6.3.2,9.6.3.3
1270552	2005, Oral toxicity (LD50) to honey bees (Apis mellifera L.); Code: AE 0172747 02 SC52 A105, DACO: 9.2.4.1
1270553	2005, Contact toxicity to honey bees (Apis mellifera L.), Code: AE 0172747 02 SC52 A105, DACO: 9.2.4.1
1270554	2005, AE 0172747 - Oral toxicity (LD50) to honey bees (Apis mellifera L.) - substance technical, DACO: 9.2.4.1
1270555	2002, AE 0172747 - Contact toxicity (LD50) to honey bees (Apis mellifera L.) - Substance technical, DACO: 9.2.4.1
1270556	2005, Tier II Seedling emergence nontarget plant study using AE 0172747 SC52, DACO: 9.8.6
1270557	2005, Tier II - Vegetative vigor nontarget plant study using AE 0172747 SC52, DACO: 9.8.6
1270558	2005, Lemna gibba G3: Growth inhibition test with AE 0456148 (Code: AE 0456148 00 1B99 0002), DACO: 9.3.5,9.5.4,9.8.5,9.8.6
1270559	2005, Duckweed (Lemna gibba G3) growth inhibition test with recovery phase - AE 0172747 - substance, technical, DACO: 9.3.5,9.5.4,9.8.5,9.8.6
1270560	2005, Pseudokirchneriella subcapitata growth inhibition limit test with AE 0456148 (code: AE 0456148 00 1B99 0002), DACO: 9.8.2,9.8.3,9.8.6
1270561	2005, Pseudokirchneriella subcapitata growth inhibition test with AE 0172747 & isoxadifen-ethyl SC 420 + 210 (code: AE 0172747 02 SC52 A105), DACO: 9.8.2,9.8.3,9.8.6
1270563	2005, Algal growth inhibition - Navicula pelliculosa - AE 0172747, substance technical, DACO: 9.8.2,9.8.3,9.8.6
1270564	2005, Algal growth inhibition - Pseudokirchneriella subcapitata - AE 0172747; substance, technical, DACO: 9.8.2,9.8.3,9.8.6
1270565	2005, AE 0172747 - Acute toxicity to the marine diatom, Skeletonema costatum, under static conditions, DACO: 9.8.2,9.8.3,9.8.6

1270566	2005, AE 0172747 - Acute toxicity test with freshwater blue-green alga (Anabaena flos-aquae), DACO: 9.8.2,9.8.3,9.8.6
1270756	2004, AE 0456148 00 1B99 0002: AE 0456148, substance pure: acute toxicity to earthworms (Eisenia fetida) tested in artificial soil, DACO: 9.2.3.1
1270757	2004, Acute toxicity (14 days) of AE 1124336 00 1B98 0001 to the earthworm Eisenia fetida in artificial soil, DACO: 9.2.3.1
1270758	2004, Acute toxicity (14 days) of AE 1392936 00 1C93 0001 to the earthworm Eisenia fetida in artificial soil, DACO: 9.2.3.1
1270759	2004, Acute toxicity (14 days) of AE 0941989 00 1B99 0001 to the earthworm Eisenia fetida in artificial soil, DACO: 9.2.3.1
1270760	2004, Acute toxicity (14 days) of AE 0968400 00 1B98 0001 to the earthworm Eisenia fetida in artificial soil, DACO: 9.2.3.1
1270761	2002, Acute toxicity to earthworms (Eisenia fetida) - AE 0172747; substance; technical, DACO: 9.2.3.1
1270762	2005, Summary of avian chronic toxicity findings and proposed avian chronic toxicity benchmark values for AE 0172747, DACO: 9.9
1270764	2005, Chironimus riparius 28-day chronic toxicity test with AE 0172747 (tech.) in a water-sediment system using spiked water, DACO: 9.9
1443019	2007, RESPONSE TO EPAs AQUATIC ECOLOGICAL AND DRINKING WATER EXPOSURE ASSESSMENTS FOR TEMBOTRIONE (AE 0172747), DACO: 9.9
1443020	2007, Tembotrione: An Assessment of Risk to Endangered Species Associated with Corn, DACO: 9.9
1581365	2005, Oral toxicity (LD50) to honey bees (Apis mellifera L.); Code: AE 0172747 02 SC52 A105, DACO: 9.2.4.1 CBI
1581366	2005, Contact toxicity to honey bees (Apis mellifera L.), Code: AE 0172747 02 SC52 A105, DACO: 9.2.4.1 CBI
1581368	2005, Acute toxicity of AE 0172747 & isoxadifen-ethyl SC 420+210 to the waterflea Daphnia magna in a static laboratory test system, DACO: 9.3.2,9.3.4,9.3.5,9.5.4,9.8.6 CBI
1581369	2005, Acute toxicity of AE 0172747 & Isoxadifen-ethyl SC 240+210 to fish (Oncorhynchus mykiss) under static conditions (product code: AE 0172747 02 SC52 A105), DACO: 9.3.5,9.4.2,9.4.3,9.4.4,9.4.6,9.5.2.1,9.5.2.2,9.5.2.3,9.5.4,9.8.6 CBI
1581370	2005, Pseudokirchneriella subcapitata growth inhibition test with AE 0172747 & isoxadifen-ethyl SC 420 + 210 (code: AE 0172747 02 SC52 A105), DACO: 9.8.2,9.8.3,9.8.6 CBI
1581371	2005, Chironimus riparius 28-day chronic toxicity test with AE 0172747 (tech.) in a water-sediment system using spiked water, DACO: 9.9 CBI

4.0 Value

1672977 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF EFFICACY TRIALS, DACO: 10.2.3,10.2.3.1

1672978 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF EFFICACY TRIALS, DACO: 10.2.3,10.2.3.1

1672979 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF EFFICACY TRIALS, DACO: 10.2.3,10.2.3.1

1672980 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF NON-SAFETY ADVERSE EFECTS, DACO: 10.3,10.3.1

1672981 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF NON-SAFETY ADVERSE EFECTS, DACO: 10.3,10.3.1

1672982 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 SUMMARY OF NON-SAFETY ADVERSE EFECTS, DACO: 10.3,10.3.1

1672983 2008, SP102000015037 SC547 Herbicide - ADDENDUM -01 Additional Data on field corn to Address a PMRA Deficiency Review Notes, subm. no. 2007-3260 - Field trials, DACO: 10.2.3.3(B),10.3.2(A)

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

1536725 2002, DACO 4.2, Published articles from American Journal of Ophthalmology; Corneal Opacities Associated With NTBC Treatment, DACO: 4.8